Stepped care for chronic fatigue syndrome

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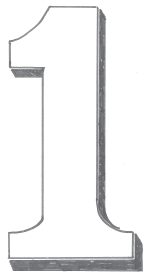


General introduction

This thesis reports on studies investigating different phases of stepped care for chronic fatigue syndrome (CFS). The studies are aimed to gain insight into the process of diagnosing CFS by a general practitioner, to test the effectiveness of implementation of different elements of stepped care and to indentify moderators of treatment response of the first step of stepped care, guided self-instruction. The overall purpose of these studies is to develop strategies to increase treatment capacity and treatment efficiency for patients with CFS. In this introduction, stepped care for CFS and the objectives for the different studies are described.

Chronic Fatigue Syndrome

Fatigue is a sensation that is hard to define. Everyone feels tired from time to time. It is a part of everyday life. However, fatigue can become a problem and interfere with daily life. Research shows that 25-30% of the complaints in general practice are fatigue related. In the general population these percentages are even higher, 30-50% report fatigue as a symptom [1-7]. In Dutch general practice, fatigue is found to be the third most common complaint [8]. Approximately 5-10% of the patients in primary care describe fatigue as their main complaint [9]. When fatigue becomes severe, lasts longer than six months, is medically unexplained, and leads to substantial impairments in daily life, a general practitioner can consider the diagnosis CFS. Chronic fatigue is defined as self-reported physical and/or mental discomfort during a period for at least six months which expresses itself in exhaustion, due to which a person is physically and/or mentally unable to function on the required level [10]. To fulfil the United States Centers for Disease Control and Prevention criteria (CDC) for CFS patients must report, aside from fatigue and disabilities, four out of eight additional symptoms: unrefreshing sleep, post-exertional malaise, headache, muscle pain, multi-joint pain, sore throat, tender lymph nodes and concentration and memory impairment [11]. In the Netherlands, it is estimated that there are 30 000 to 40 000 patients with CFS [12]. A recently published study suggests that there are even more people with CFS. They estimate that 1% of the general population, i.e., 128 500 adults, in the Netherlands meet the CDC criteria for CFS [13].

Diagnosing CFS

General practitioners are able to diagnose CFS. However, knowledge about how to diagnose CFS is limited among general practitioners and negative attitudes towards CFS exist, preventing it from being diagnosed [14, 15]. Not diagnosing CFS causes harm as there are effective treatments for CFS. Spontaneous recovery of CFS occurs in only 5% of the patients [16]. Therefore, effective management of CFS is only possible if general practitioners are able to diagnose CFS, resulting in an accurate referral for treatment. Scheeres et al.

evaluated the impact of informational interventions on general practitioners referrals of CFS patients [17]. They found that repeated written information about CFS had a clear impact on referral behaviour. General practitioners who had read the information reported that they had better knowledge about CFS and had a more positive attitude towards diagnosing CFS. Although providing information increased the number of referrals for treatment for CFS—based on data of the Dutch Health Council—the number of CFS patients living in the region was estimated five times higher than the actual number of patients that was referred to the mental health centre (MHC) [12, 18]. A study investigating the prevalence of fatigue—based on the data of the Nijmegen Biomedical Study—reported that of the patients fulfilling the criteria for CFS, only 6.7% (6 out of 89) was diagnosed as having CFS [13]. Both studies implicate that general practitioners' knowledge about how and when to diagnose CFS is limited [13, 17]. This suggests that correctly diagnosing CFS—which enables a referral for treatment—is necessary to improve the prognosis of CFS patients.

Cognitive Behaviour Therapy is effective

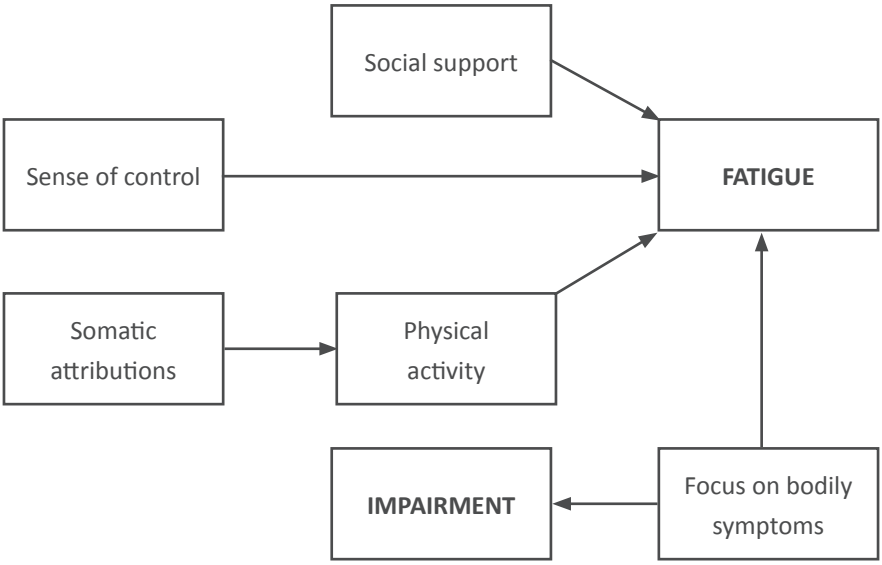
Systematic reviews of treatments for CFS, including behavioural, pharmacological, and complementary approaches conclude that cognitive behaviour therapy (CBT) is an effective approach. CBT for CFS leads to significant improvement of fatigue and impairments in CFS patients [19-22]. Some patients even fully recover [23].

CBT is aimed at the perpetuating cognitive and behavioural factors of CFS. Perpetuating factors are factors that maintain fatigue. In CBT for CFS the focus lies on changing dysfunctional fatigue related cognitions and in gradually increasing daily activities. The treatment protocol used by our tertiary treatment centre, the Nijmegen Expert Centre for Chronic Fatigue, is based on the model of perpetuating factors introduced by Vercoulen et al. [24]. The model assumes that the belief that symptoms have a physical cause can lead to a reduction of physical activity, which results in the perpetuation of fatigue and disabilities. Also a lower sense of control over symptoms, also called self-efficacy, and a strong focus on bodily symptoms can perpetuate fatigue and impairments. A later study showed that a lack of social support had a negative influence on the level of fatigue [25] (Figure 1). The efficacy of CBT for CFS—based on this model—is demonstrated in several trials [23, 26-28].

Treatment protocol of CBT for CFS

The aim of CBT for CFS is reducing fatigue and disabilities by changing fatigue-related cognitions and behaviours. CBT for CFS starts with the establishment of goals and explaining the model of perpetuating factors to the patient. When formulating the treatment goals, it is explained to the patient that recovery is possible. Recovery means that a patient no

Figure 1: Model of perpetuating cognitions and behaviour of CFS



longer suffers from CFS, in other words: is no longer severely fatigued and disabled, and can resume 'normal' activities as a result of the therapy. At the start of CBT, recovery will be defined in concrete behavioural terms leading to concrete treatment goals. Next, fatigue related cognitions are changed. Patients are helped to reduce the focus on bodily symptoms and to develop a sense of control over their symptoms. In addition, patients start to regulate their sleep-wake cycle and learn how to divide their activities more evenly over the day. After this, patients start with a graded activity program consisting of walking or cycling. Patients with low physical activity levels do not have to divide their activities first, they immediately start with a build up of their activity level. Through this graded activity program, dysfunctional illness beliefs, e.g. the thought that activity will increase the severity of fatigue, are challenged, while avoidance behaviour is reduced. Supplementary, patients learn how to deal with the reaction of their social environment regarding their symptoms and to increase mental and social activities. By gradually increasing their activities, patients will experience more sense of control over their symptoms. Once patients have increased their activities to an adequate level, they start to systematically accomplish their personal goals as set at the beginning of the therapy. The treatment ends with interventions aimed at the prevention of relapses.

Stepped care for CFS: less is more

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Implementation of stepped care for CFS

It has been shown that therapists with no previous clinical experience in treating CFS patients, can perform CBT for CFS effectively with training and supervision [27]. This suggests that the intervention can be transferred from an academic treatment setting into clinical practice settings. As a first step toward nationwide implementation, our centre performed a pilot implementation project that took place in an MHC. Results demonstrated that CBT for CFS can be successfully implemented in an MHC. Effect sizes for fatigue severity and disabilities were within the 95% confidence interval of a statistical benchmark, meaning that the results of the pilot implementation were similar as to those found in randomised controlled trials testing the effectiveness of CBT for CFS [34]. However, besides training and supervision additional actions were necessary for success. This entailed monthly project group meetings and the presence of a researcher who performed interventions aimed at the encountered problems. On the basis of the gained experiences an implementation manual was developed to maximise success of future implementation projects. The underlying idea of this manual was that future implementation projects can anticipate at the expected problems and can profit optimally from the experiences learned in the past.

Outline of the thesis

Implementation of stepped care for CFS is only possible if general practitioners are favourable disposed to recognise and diagnose CFS. However, several studies suggest that CFS may be under diagnosed in primary care [5, 13, 18]. *Chapter 2* describes a study that investigates the ability of general practitioners to diagnose CFS in primary care. In a prospective and retrospective cohort it is investigated how many patients experiencing fatigue fulfilled the criteria for CFS and are diagnosed as such by a general practitioner.

In *chapter 3* the effectiveness of a model of stepped care for CFS—guided self-instruction followed by additional individual face to face CBT if necessary—is tested. In a randomised controlled trial stepped care is compared to care as usual—individual regular face-to-face CBT after a waiting period. To gain more insight in the efficiency of stepped care and care as usual, the number of individual CBT sessions and the total therapist time required in both conditions are compared. This study is undertaken at the Expert Centre for Chronic Fatigue, a tertiary treatment centre.

Besides developing stepped care for CFS, treatment capacity can also be enhanced if other disciplines instead of fully trained cognitive behavioural therapists are able to deliver the treatment. In a randomised controlled trial it is tested whether the minimal intervention is also effective when implemented in a community based MHC. Psychiatric nurses, unacquainted with CFS and the treatment of CFS, received a short training and supervision to support patients during guided self-instruction. The results of the minimal intervention on fatigue and impairment in physical functioning and social functioning are reported in *chapter 4*.

Efficiency of guided self-instruction can be further improved if it is known which patients are likely to benefit from the minimal intervention. To understand the variability of outcome in psychological interventions, moderators of treatment response can be identified. Moderators are variables that influence treatment outcome. In *chapter 5*, first potential moderators are selected from the literature. Second—based on the selection—potential moderators of treatment response to guided self-instruction are tested.

The study presented in *chapter 6* evaluates the implementation of CBT for CFS in three different MHCs based on the guidelines and experiences as described in the implementation manual. One MHC implements CBT for CFS as only intervention, the second MHC implements CBT in the context of stepped care for CFS and the third MHC evaluates if effects from an earlier implementation of CBT can be sustained. Prior to the start of the implementation the

criteria for successful implementation are determined. During project group meetings with all those involved, the progress of the implementation is evaluated.

Finally *chapter 7*, entails a general discussion which consists of two parts. In the first part of the discussion the practical implications of the findings are discussed. In the second part findings are discussed in the context of relevant existing literature on (implementation of) treatment for CFS and recommendations for future research are formulated.

Expert Centre for Chronic Fatigue

The studies reported in this thesis are carried out at the Expert Centre for Chronic Fatigue of the Radboud University Nijmegen Medical Centre. Several disciplines, among others internists, pediatricians, virologists, oncologists, neurologists, neurophysiologists, neuroscientists and psychologists, collaborate to increase the expertise in chronic fatigue. Studies focussing on the somatic and psychological factors and consequences of CFS resulted in a model of perpetuating factors. This model is the basis of the protocol of CBT for CFS [24]. Through the years the model has been refined and improved as well as the treatment. Current research focus on nationwide implementation of a model of stepped care for CFS, the development of new interventions like internet therapy and research into the neurobiological correlates of CFS.

Besides CFS, the Expert Centre for Chronic Fatigue, also performed research on chronic fatigue in cancer [35, 36], neuromuscular disorders [37, 38], rheumatoid arthritis [39] and other conditions [40-43]. New treatment protocols were developed and adapted for disease-specific factors. For example, it has been shown that CBT is effective in reducing fatigue in disease-free cancer patients. For more information see the website: www.umcn.nl/research/departments/eccf.

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The challenge of diagnosing CFS in primary care

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Fatigue is highly prevalent in general practice [1]. Approximately, 5-10% of the patients in primary care present fatigue as their main complaint [2]. If this fatigue is medically unexplained, prolonged and disabling the diagnosis chronic fatigue syndrome (CFS) can be considered. For effective management of CFS, it is necessary to make an accurate—preferably early—diagnosis, resulting in a suitable referral. Managing the condition will help to improve the quality of care for CFS patients [3, 4]. However, CFS is more common in primary care than recognised [5]. Although some general practitioners (GPs) are aware of the usefulness of the label CFS, other GPs express scepticism and negative attitudes towards diagnosing it [6-8]. This study was performed to gain insight in the ability of GPs to diagnose CFS.

We performed a prospective and retrospective patient cohort study in a general practice group caring for ± 8000 patients. Patients, aged between 18-70 years, visiting the practice during the research period (four weeks) and patients who had presented fatigue one year ago, were examined to fill out a questionnaire assessing fatigue. Fatigue was measured with the Shortened Fatigue Questionnaire [9]. Physical and social disabilities were measured with the Medical Outcome Survey Short Form-36 [10]. When patients were chronically fatigued and severely disabled, their electronic medical files were examined to exclude alternative explanations for their fatigue. Next, a specialist was asked to diagnose each patient as CFS or non-CFS.

Almost 31% of the adult population visiting their GP (n = 500) reported complaints of fatigue. Of the patients presenting complaints of fatigue in the past (n = 111), still 50% had complaints of fatigue one year later. In the prospective cohort, 2% (18/500) of the patients were assumed to fulfil the criteria for CFS based on the United States Centers for Disease Control and Prevention. In the retrospective cohort, 8% (19/111) of the patients could be classified as having CFS. One person was actually diagnosed by his GP as having CFS.

The results of this study suggest that GPs have difficulties in diagnosing CFS. There is a discrepancy between the number of patients that might be considered as having CFS and the actual number of patients that is diagnosed with CFS. Although, information is missing about the interactions between GPs and patients presenting with fatigue, we conclude that this discrepancy is unfavourable. It results in under diagnosis and therefore under treatment of CFS in primary care. Based on the information in the electronic medical files, GPs mostly interpret fatigue as a symptom of psychosocial problems. They consider the psychosocial problem as the central issue and expect that attention limited to the somatic aspects of complaints, such as fatigue, hinders the solution of these problems. As there are effective

treatments for CFS, not diagnosing CFS means withholding the patient from the possibility to recover. The data emphasise that it is necessary to develop a model of support for GPs, which results in an increase in confidence to diagnose CFS. The provision of instruments, education and services to diagnose CFS can contribute to this situation.

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Effectiveness of stepped care for chronic fatigue syndrome: a randomised noninferiority trial

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Abstract

In this randomised noninferiority study the effectiveness and efficiency of stepped care for chronic fatigue syndrome (CFS) was compared to care as usual. Stepped care was formed by guided self-instruction followed by cognitive behaviour therapy (CBT) if the patient desired it. Care as usual encompassed CBT after a waiting period.

A total of 171 CFS patients were randomly allocated to stepped care or care as usual. Patients in both conditions were assessed three times: at baseline, after guided self-instruction, or during the waiting period and after CBT. The primary outcome variables were fatigue severity (Checklist Individual Strength) and disabilities (Sickness Impact Profile and Medical Outcomes Survey Short Form-36).

An intention to treat analysis showed that stepped care (n = 84) for CFS is noninferior to care as usual (n = 85). Both conditions were equivalent in reducing fatigue severity, reducing disabilities and increasing physical functioning. The treatment results of both conditions were in accordance with those of previous randomised controlled trials testing the effectiveness of CBT for CFS. The total therapist time needed to treat a patient was significantly less in the stepped care condition.

Stepped care is as effective as CBT and is more time efficient for the therapist.

Introduction

Chronic fatigue syndrome (CFS) is characterised by severe fatigue that lasts longer than six months and leads to functional impairments. It is not the result of an organic disease or ongoing exertion and not alleviated by rest [1]. Besides severe fatigue and considerable functional impairments, most patients report additional symptoms. According to the CFS criteria of the US Centers for Disease Control criteria [1], a patient must report four out of eight additional symptoms: unrefreshing sleep, postexertional malaise, headache, muscle pain, multi-joint pain, sore throat, tender lymph nodes and concentration and memory impairment.

Cognitive behaviour therapy (CBT) is an evidence-based treatment for CFS [2]. Two recent meta-analyses showed that CBT for CFS leads to a reduction in fatigue and disabilities [3-5]. Besides, The natural course of CFS without treatment is unfavourable; only 5% of the patients recover spontaneously [6]. CBT is not only superior to no intervention but is also more effective than guided support groups or relaxation training [7, 8].

CBT is directed at changing fatigue-related cognitions and behaviours that perpetuate fatigue at least to a significant degree. The treatment is aimed at decreasing the focus on bodily symptoms, increasing self-efficacy with respect to fatigue, changing the way patients communicate about CFS, regulating and/or increasing physical activity, and changing their attitude when dealing with the way others react to their symptoms. Recent research has shown that CBT is not only effective in randomised controlled trials (RCTs) conducted in tertiary university hospitals but can also be successfully implemented in a representative clinical practice setting [9]. However, wider implementation is hampered by the fact that CBT for CFS is an intensive treatment that requires 13 to 16 sessions, depending on the protocol used [7, 10, 11]. Licensed cognitive behaviours therapists need additional training and supervision to learn to treat CFS. In addition, the treatment capacity in the Netherlands is lacking [12].

It is probable that not all patients need such an intensive treatment as CBT, which would make it possible to develop a form of stepped care. In stepped care, more intensive treatments are reserved for patients who do not benefit from simpler low-intensity treatments or for those who can be predicted not to benefit from such treatments [13]. In the literature, it has already been proven that stepped care is effective for psychological interventions [14]. It has also been shown that for patients with chronic fatigue, a self-help booklet with support from a nurse was more effective than no treatment [15]; a minimal intervention for patients with CFS, consisting of psycho-education and a graded activity program, decreased the levels of

fatigue and disabilities compared with a control condition [16, 17]. For stepped care for CFS, it is necessary to develop a less intensive intervention based on the CBT protocol which can be followed by additional CBT.

Recently, we showed in an RCT [18] that a minimal CBT intervention for CFS leads to a significant reduction of fatigue and disabilities compared with a waiting list. Twenty-seven percent of the patients showed a clinically significant improvement during treatment. Instead of 13 to 16 sessions, the minimal intervention consisted of a self-instruction booklet based on the CBT protocol for CFS and email contact with a therapist every two weeks. This minimal intervention (i.e., guided self-instruction) could be the first step of stepped care, followed by additional treatment with individual CBT if the minimal intervention did not suffice. If stepped care can be applied in the treatment of CFS patients–which means that patients get the intensity of treatment necessary to improve, no more and no less–more CFS patients can receive treatment for their condition.

As a second stage of the previously described trial [18], we performed an explanatory randomised noninferiority follow-up study in which we offered all patients individual CBT after the minimal intervention or waiting list. The main objective of the study was to compare the effectiveness of stepped care (self-instruction, possibly followed by additional CBT) to care as usual (only regular CBT after a waiting list). In other words, as this is a noninferiority trial, we determined whether stepped care was no worse in reducing fatigue and disabilities than care as usual. To evaluate the treatment effect of both conditions, outcomes were compared with those of previous RCTs testing the effectiveness of CBT for CFS [9].

Furthermore, in an exploratory analysis the efficiency of both conditions was compared. First we compared the number of individual CBT sessions, and then we compared the total therapist time required in both conditions. During the minimal intervention, patients had already received information about their disorder and about the symptom perpetuating factors. So, we expected that the informed patient would need fewer sessions of CBT than the patients who received CBT for CFS after the waiting list. Therefore, the time a therapist needed to deliver stepped care or care as usual could be less in the stepped care condition.

Method

Participants

All patients had participated in the RCT testing the effectiveness of guided self-instruction [18]. They were referred for CBT to the Expert Centre for Chronic Fatigue of the Radboud University Nijmegen Medical Centre, a tertiary treatment facility. Patients were 18 years

or older; spoke and read Dutch; had undergone a medical and psychiatric evaluation that excluded other causes of fatigue; fulfilled the US Centers for Disease Control criteria for CFS [1]; were severely fatigued, operationalised as scoring 35 or more on the Fatigue Severity of the Checklist Individual Strength (CIS) [19]; and were severely disabled, operationalised as having a total score of 700 or higher on the Sickness Impact Profile [20].

Patients were temporarily excluded from therapy for as long as they were engaged in a legal procedure concerning disability-related financial benefits. This was done because a previous intervention study had shown that being engaged in such a procedure predicted a negative treatment outcome [21] (See Table 1).

Design and procedures

In the original study [18], patients applying for individual CBT were recruited from February 2006 to September 2007. First, patients received a baseline assessment; when criteria for CFS were met, they were offered CBT. Because of limited treatment capacity, patients who

Table 1. Baseline characteristics

Baseline characteristics	Stepped care (*n* = 84)	Care as usual (*n* = 85)	*t*-value$_{(167)}$	*P*
Demography				
Age, means (*SD*)	37.6 (10.0)	38.5 (10.6)	-0.55	0.58
Duration of complaints (months, median (min-max))	72 (12,420)	96 (12,420)	-1.22	0.23
Male/Female	15 /69	20 /64	χ^2=0.83	0.36
Outcome measures, means (*SD*)				
CIS fatigue severity	49.11 (5.2)	49.9 (5.6)	-0.96	0.34
SIP total score	659 (648)	1515 (545)	1.56	0.12
SF-36 physical functioning	52.3 (20.4)	54.1 (21.1)	-0.56	0.58
Indices of severity, means (*SD*)				
Number of CDC symptoms	7.1 (1.6)	7.3 (1.6)	-0.58	0.57
Perpetuating factors, means (*SD*)				
Activity pattern (passive/active)	24 /60	20 /65	χ^2=0.56	0.46
Self efficacy	17.4 (3.2)	17.9 (2.8)	-0.99	0.33
Somatic attributions	12.4 (2.9)	12.0 (3.2)	0.86	0.39
Focusing on bodily symptoms	28.7 (8.1)	29.6 (8.3)	-0.68	0.50

CIS, Checklist Individual Strength; SIP8, Sickness Impact Profile; SF-36, Medical Outcomes Survey Short From-36; CDC, Centers for Disease Control.

accepted the treatment that was offered were placed on a waiting list (6 to 12 months). Patients were then given verbal and written information about the study. They were told that while they waited for CBT, they could participate in a study testing the efficacy of a minimal intervention, which would not lead to a longer waiting period for individual therapy. If informed consent was obtained, patients were randomly allocated to the minimal intervention or the waiting list. Allocation to condition was carried out by the therapist using cards in consecutive numbered and sealed envelopes that were opened in the presence of the patient. An independent statistical advisor prepared the envelopes by coding them according to a computer-generated list of random numbers. Randomisation was performed in blocks of eight. After the minimal intervention or waiting list, the patient decided whether CBT was still desired. Patients in both conditions were assessed three times: (a) at baseline; (b) directly following the guided self-instruction or waiting period; and (c) after additional CBT (stepped care) or regular CBT (care as usual). When a patient did not want treatment after the minimal intervention or waiting period, there were only two assessments: at baseline and after the minimal intervention or waiting period.

Intervention

The minimal intervention was based on a published protocol of CBT for CFS [22]. The treatment starts with establishing goals and explaining the model of perpetuating factors to the patient. Next, fatigue-related cognitions are challenged to diminish somatic attributions, to decrease the focus on bodily symptoms, to improve sense of control over symptoms, and to facilitate behaviours change. At the same time, a structured physical activity program starts. After regulating and/or increasing activity, a work rehabilitation plan or a rehabilitation plan in other personal activities was developed. The therapy ends with interventions aimed at the prevention of relapses and further improvement of self-control.

In the minimal intervention, patients received a self-instruction booklet with information about CFS and assignments. In this booklet the patient could follow the instructions week by week. The total program took at least 16 weeks but could take more time if the patient wanted to reach goals like resumption of work. The booklet was given to the patient after randomisation. The therapist invited the patient to email at least every two weeks, to report on the progress and ask questions about the self-instruction. Patients were told that they were free to email more frequently if they wanted. If a patient was not able to email, the therapist proposed that the patient phone at least every two weeks. After the minimal intervention, each patient had a face-to-face session with the therapist to discuss whether additional CBT was desirable.

Regular CBT was delivered according to the protocol described by Bleijenberg et al. [22]. The treatment consisted of 14 sessions over a period of six months. The highest attainable goal of CBT is recovery, which means (a) no longer being severely fatigued and (b) no longer being disabled by the fatigue. In addition, the therapist discussed with the patient whether his or her view was no longer that of a CFS patient. This can lead to variation in the number of sessions. Both interventions, guided self–instruction and CBT, were carried out by the same cognitive behavioural therapists (*n* = 5).

In both interventions there were two treatment protocols, depending on the pattern of physical activity of the patient. This activity pattern was assessed with an actometer, a motion sensing device that can quantify human physical activity. The actometer was worn around the ankle during a 14-day period to retain 12 complete registration days. From this registration period a relatively active or a passive pattern can be established. A passive CFS patient has an average daily activity score below the norm score of CFS patients (norm score = 66) on 11 or 12 of a total of 12 days [23]. Patients with a relatively active physical activity pattern alternate between periods of activity and periods of rest. These patients have to attain a base level of activity, where they spread their activities more evenly over the day. After they have achieved this, they gradually increase their activity level and resume work and other activities. Patients with a passive activity pattern are continuously physically inactive. They immediately start with the graded activity program. Patients with a relatively active or passive pattern were evenly grouped between stepped care and care as usual (See Table 1).

Outcome measures

Fatigue. Fatigue was measured with the Fatigue Severity subscale of the CIS [19]. This subscale indicates fatigue, which is central in CFS patients, over the past two-week period with scores ranging between 8 (no fatigue) to 56 (severe fatigue). The CIS is a reliable and valid instrument for assessment of fatigue in CFS [24].

Disabilities. The level of disability was measured in two ways. The Sickness Impact Profile was used to measure functional disability in ambulation, home management, mobility, alertness behaviours, sleep and rest, work limitations, social interactions, recreation, and pastimes [20]. A weighed total score was computed from the scores on the eight subscales. Physical disabilities were measured with the Physical Functioning subscale of the Medical Outcomes Survey Short Form-36 (SF-36) [25]. The scores ranged from 0 (maximum limitations) to 100 (no limitations).

Clinically significant improvement. Clinically significant improvement was defined as a reliable change index > 1.96 [26] between baseline and post-treatment and a score of < 35 on the CIS Fatigue Severity subscale at post-treatment assessment. This latter score is within two standard deviations of the mean for healthy adults and below two standard deviations of the mean for CFS patients [27].

Number of therapy sessions. For both conditions, stepped care and care as usual, the number of individual CBT sessions was counted (including 2 assessment sessions).

Total therapist time. To compare the efficiency of both conditions, the time therapists needed to deliver stepped care and care as usual was calculated. In the stepped care condition, this consisted of two assessment sessions of 60 min, the time needed to write emails, and the individual CBT sessions (duration = 60 min). The time needed to write emails was calculated by counting the number of emails sent by the therapist and multiplying this by the average time needed to write one email. For this, the therapists estimated retrospectively the mean time they needed to write an email. If patients used the telephone or both email and telephone (in case patients did not react on the emails sent by the therapist), or if data were missing, it was assumed that this would cost the therapist the same amount of time as treating patients who only emailed. In the care as usual condition, the number of individual CBT sessions was multiplied by 60 min (including two assessment sessions). If a patient did not start treatment, only two assessments sessions were calculated.

Analysis

Analyses were performed using SPSS (version 16) for Windows. Statistical significance was assumed at $p < .05$. The two conditions were regarded as equivalent if the difference in CIS fatigue severity (using 95% CI) was less than 5.2 points and there were no significant differences on the other two outcome measures, disabilities and physical functioning. The boundary of 5.2 points was derived from the 95% CI of the change in CIS fatigue severity score that occurred in the waiting list condition in the prior study [18].

To test for differences between the two conditions, an analysis of covariance (ANCOVA) was used, with the scores on fatigue severity and level of disabilities directly after CBT as dependent variable, the baseline scores as covariate, and the condition as fixed factor (2 levels: stepped care vs. care as usual). An ANCOVA was used because treatment allocation is by randomisation. In this kind of trial, ANCOVA yields greater power than other statistical methods [28]. A logistic regression model was used to estimate differences between the two conditions in the proportion of patients with a clinical significant improvement of

fatigue. All comparisons were performed on the basis of intention to treat. We used multiple imputation (using the MICE package) [29] in R (Version 2.9.2) [30] to handle the missing observations. In total, 100 imputed datasets were generated. The imputation method used was predictive mean matching for all variables with missing data. We used age, condition, baseline measurements, measurements after the minimal intervention or waiting period, and post-treatment measurements to generate the imputations. The pooling of the results was done according to Rubin's rules [31], using the small sample correction of Barnard and Rubin [32].

A second logistic regression with condition and baseline CIS fatigue as predictors was used to test for differences between (a) only guided self-instruction and stepped care and (b) only guided self-instruction and care as usual in the proportion of patients with a clinical significant improvement of fatigue. Results of guided self-instruction were adopted from the earlier study of Knoop et al. [18].

In a post-hoc analysis, independent sample *t* tests were used to test for differences at baseline in the outcome variables and demographic characteristics between patients who either did or did not continue with CBT after guided self-instruction.

To evaluate the effectiveness of stepped care and care as usual, outcomes were compared with those of previous RCTs testing the effectiveness of CBT for CFS. In a statistical benchmark [9], we calculated the mean effect size for fatigue severity (CIS; 1.44; 95% CI [0.97-1.89]) and physical functioning (SF-36; 1.04 95% CI [0.63-1.44]) of CBT in four RCTs. The pre-post test effect size of stepped care and care as usual was calculated ((M start – M end) / SD start) [33] and compared to the statistical benchmark. If the effect sizes of a condition fell within the 95% CI of the mean effect size of the benchmark study for both fatigue severity and physical functioning, the condition was considered to meet the benchmark.

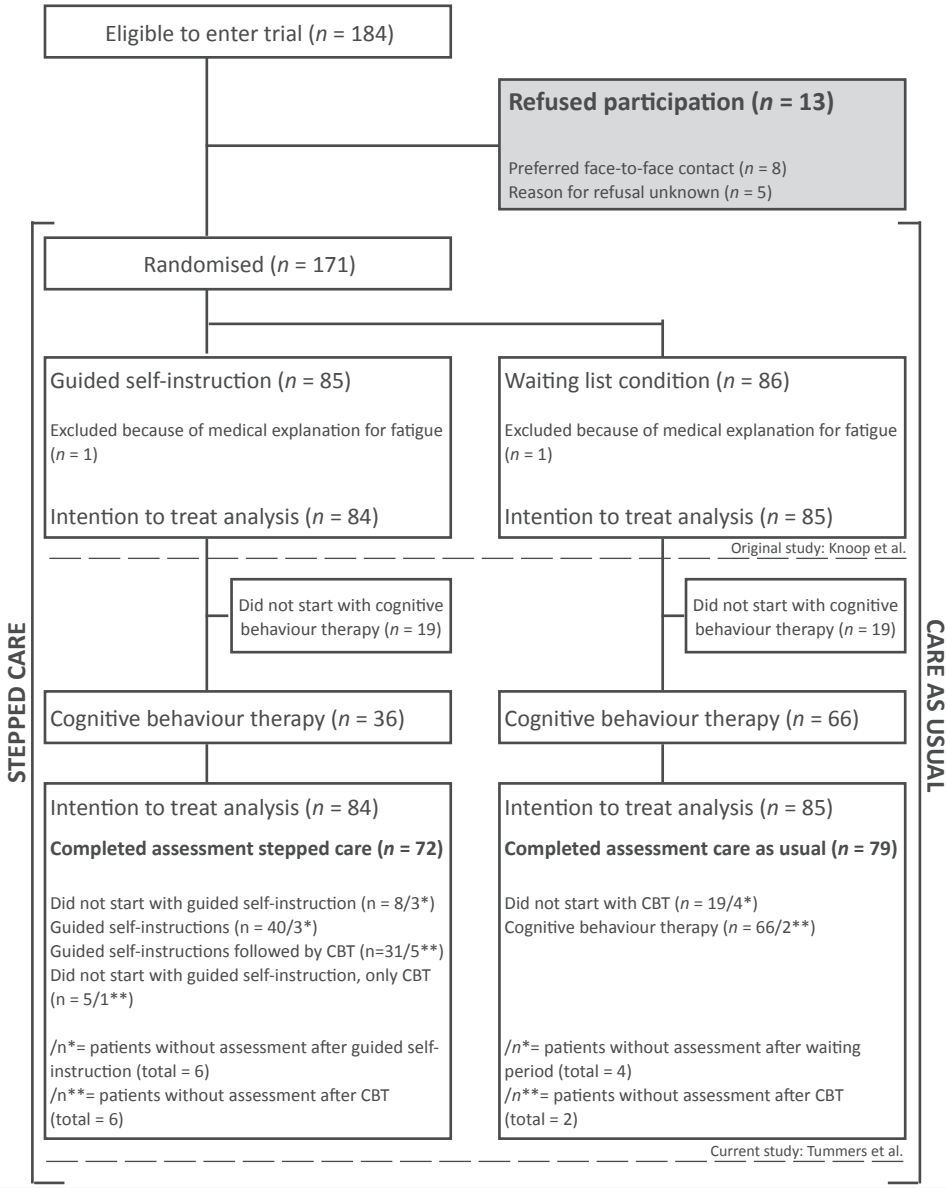
Differences in number of CBT sessions and total therapist time for stepped care and care as usual were tested with the Student *t* test and Mann-Whitney *U* test, respectively.

Results

In the original study [18], 171 patients were randomly allocated to guided self-instruction (*n* = 85) or a waiting list (*n* = 86). Two patients were excluded because another medical condition was diagnosed after randomisation. After the minimal intervention or waiting list, all patients were offered CBT. Forty-eight patients of the guided self-instruction condition and 19 patients of the waiting list condition declined the offer for further therapy. In the

stepped care condition, six patients had no assessment after guided self-instruction, and six patients had no assessment after CBT. In the care as usual condition, four patients had incomplete data after the waiting period and two after CBT. There were 72 (86%) patients with complete data after stepped care and 79 (93%) patients after care as usual (See Figure 1).

Figure 1. Flow of participants through the study



Comparison of the effectiveness

The difference in fatigue severity between the two groups was 0.2 (95% CI [-3.9 to 4.4]). On the basis of the analyses, stepped care was declared noninferior to care as usual because the upper bound of the 95% CI (4.4) was within the critical interval for determining noninferiority (+5.2). There were no significant differences between stepped care and care as usual for fatigue severity, disabilities and physical functioning (See Table 2). The logistic regression showed that there were no significant differences between stepped care and care as usual for clinically significant improvement in fatigue at the post-treatment assessment (See Table 3).

The second logistic regression showed that after guided self-instruction, the proportion of patients with a clinical significant improvement was significantly smaller compared to stepped care, $\beta = 0.39$, χ^2 (2, n = 168) <0.01, and care as usual, $\beta = 0.35$, χ^2 (2, n = 169) <0.01.

Comparisons of post-hoc analysis

Table 4 describes baseline demographic characteristics and outcome measures for the patients who either did or did not continue with CBT after guided self-instruction. There were no significant differences between those two groups for age, gender, fatigue severity, and physical functioning. Patients who continued with CBT after guided self-instruction reported significantly more disabilities ($p < .01$) at the baseline measurement (See Table 4).

Effect size

The effect size for stepped care was 1.37 for fatigue severity and 0.88 for physical functioning. For care as usual this was 1.42 and 0.70, respectively. Both effect sizes are within the 95% CI of the benchmark.

Comparison of the number CBT sessions

After guided self-instruction, patients (n = 36) needed a mean of 10.9 CBT sessions, compared with 14.5 sessions in the care as usual condition (n = 66, $p < .01$; see Table 5).

Table 2. Change in Outcome Between Baseline and Post-treatment Assess[1]

	Stepped care (*n* = 84)		Care as usual (*n* = 85)					
Outcome measure	Baseline Mean (*SD*)	Post-treatment assessment Mean (*SD*)	Baseline Mean (*SD*)	Post-treatment assessment Mean (*SD*)	Difference Mean (95% CI)	*df*	*F*	*p*
CIS fatigue severity	49.1 (5.2)	35.2 (13.6)	49.9 (5.6)	35.0 (13.9)	0.3 (-3.8 to 4.4)	146	0.15	0.88
SIP8 Total score	1659 (648)	848 (642)	1515 (545)	854 (696)	71.1 (-109 to 251)	141	0.78	0.44
SF-36 physical functioning	52.3 (20.4)	71.3 (23.5)	54.1 (21.1)	71.9 (24.7)	-0.61 (-6.8 to 5.6)	144	-0.20	0.84

CIS, Checklist Individual Strength; SIP8, Sickness Impact Profile; SF-36, Medical Outcomes Survey Short From-36; CI, confidence interval; *df*, degrees of freedom. [1] The data slightly differ from the published article to compensate for some imperfections.

Comparison of the total therapist time

Of the 84 patients in the stepped care condition, 70 patients had contact with their therapist; 55 (66%) emailed, five (6%) used the telephone exclusively, and 10 (12%) used both email and telephone. The remaining 14 (17%) patients did not contact the therapist, 13 of them did not start with the guided self-instruction, and one completed the program without assistance of a therapist [18]. For two patients the number of emails sent by the therapist were missing. In these cases, the mean number of emails sent by all therapists was filled in. The same was done for patients who exclusively used the telephone or used email and telephone to contact their therapist. The therapists sent a mean of 8.9 (*SD* = 6.4) emails per patient and spent a mean of 22 min (range: 15-30) writing an email. Taking the number of CBT session into account, the total therapist time needed per patient was significantly lower in the stepped care condition (median = 420 min) compared to care as usual (median = 720 min, p = .01; See Table 6).

Table 3. Comparison of Proportion of Clinical Significant Improvement in CIS fatigue Severity Between Conditions

Outcome measure	Stepped care (n = 84)	Care as usual (n = 85)	OR (95% CI)	t-value$_{(153)}$	P
CIS fatigue severity, proportion %	41/84 (49%)	41/85 (48%)	1.00 (0.53 to 1.89)	0.00	1.00

CIS, Checklist Individual Strength; OR, odds ratio; CI, confidence interval.

Table 4. Post-hoc Analysis of Baseline Outcome Measures

Baseline characteristics	No CBT after guided self-instruction (*n* = 48)	CBT after guided self-instruction (*n* = 36)	*t*-value$_{(82)}$	*P*
Demography				
Age	37.8 (9.5)	37.0 (10.8)	-0.38	0.71
Male/Female	7 /41	8 /28	χ^2=0.82	0.37
Outcome measures				
CIS fatigue severity	48.1 (4.9)	50.3 (5.3)	1.93	0.06
SIP total score	1483 (948)	1893 (578)	3.05	<0.01
SF-36 physical functioning	54.1 (21.4)	50.0 (19.1)	-0.92	0.37

CIS, Checklist Individual Strength; SIP8, Sickness Impact Profile; SF-36, Medical Outcomes Survey Short From-36.

Table 5. Number of Therapy Sessions

Outcome measure	Stepped care (*n* = 36)	Care as usual (*n* = 66)	*t*-value$_{(100)}$	*P*
Number of therapy sessions during CBT (mean; *SD*)*	10.9 (4.4)	14.5 (5.3)	-3.4	<0.01

* Including 2 assessment sessions

Table 6. Total Therapist Time

Outcome measure	Stepped care (*n* = 84)	Care as usual (*n* = 85)	*u*-value$_{(100)}$	*P*
Therapist time in minutes (median; min-max)*	420 (120 – 1440)	720 (120 – 2040)	-2.4	0.01

* Including 2 assessment sessions

Discussion

This study showed that stepped care for CFS was statistically equivalent to care as usual in reducing fatigue severity and level of disabilities and increasing physical functioning. The results indicate that stepped care is noninferior to care as usual, as the upper limit of the 95% CI for the difference between stepped care and care as usual was 4.4 (boundary was 5.2). The treatment results of stepped care and care as usual are in accordance with those of previous RCTs testing the effectiveness of CBT for CFS [9]. We infer from the fact that the percentage of subjects with clinically significant improvement after guided self-instruction (27%) [18], is considerably less than after stepped care (49%, $p < .01$), that it is possible to profit from additional CBT after the minimal intervention. When guided self-instruction was not sufficient, fewer sessions of CBT were required in subsequent treatment. This suggests that if the minimal intervention does not lead to (sufficient) reduction of symptoms, it does prepare patients for subsequent CBT. Finally, therapists needed less time to treat a patient in the stepped care condition compared with care as usual, indicating that stepped care is more time efficient for therapists.

A limitation of this study is the fact that a waiting period preceded CBT in the care as usual condition. Powell et al. [16] found that a delay in treatment of CFS patients is associated with reduced efficacy. However, this does not seem to be the case in the present study, as the effect size of care as usual corresponded with the statistical benchmark [9].

Patients were offered additional treatment after the minimal intervention or regular CBT after the waiting period, regardless of the current level of complaints. In a session with their therapist, patients decided whether (additional) CBT was desirable. After guided self-instruction, 48 patients declined the offer for additional CBT. Nineteen patients did not want regular CBT after the waiting period. When a patient decided not to receive further treatment only two assessments were available: the baseline assessment and the assessment after guided self-instruction or the waiting list. Therefore, the period between baseline and post-treatment assessment could show large variability.

We did not test the treatment integrity of guided self-instruction and CBT. However, the five therapists who delivered both treatments were all well trained and experienced in delivering CBT for CFS. Therapists were supervised once every two weeks throughout the trial. The fact that the treatment results of both conditions, stepped care and care as usual, are in accordance with other trials supports the assumption that both interventions, guided self-instruction and CBT, were of good quality.

The calculation of the time spent by the therapist could be criticised. The mean time therapists needed to write an email was asked retrospectively and is therefore only an estimation of the actual time spent by the therapist. Furthermore, no data were available when patients used the telephone during the minimal intervention. It could be that communicating with patients by telephone takes more therapist time. This might have led to an underestimation of the therapist time per treated patient, making stepped care seem more time efficient than it is.

Finally, in our study qualified cognitive behavioural therapists, all of whom were psychologists working in a specialist centre, delivered the interventions. In the Netherlands, CBT is delivered by cognitive behavioural therapists. Whether other health care professionals–for example, psychiatric nurses with fewer psychotherapeutic qualifications–would be able to effectively guide CFS patients is unknown. If this were possible, it would probably lower the costs of stepped care. Therefore, in a current trial we are testing the effect of the minimal CBT intervention delivered by nurses.

To our knowledge, this is the first time the effectiveness of stepped care for CFS has been evaluated. The results showed that stepped care for CFS is as effective as care as usual, but is more time efficient. Stepped care makes it possible to increase the available treatment capacity, while providing an intervention more tailored to the needs of the individual patient.

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Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomised controlled trial

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Abstract

Cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS) is an effective but intensive treatment, requiring trained therapists. A minimal intervention based on CBT for CFS, guided self-instruction, was shown to be an effective treatment when delivered in a tertiary treatment centre. Implementing this intervention in a community-based mental health centre (MHC) will increase the treatment capacity for CFS patients. This study evaluated the effectiveness of guided self-instruction for CFS implemented in an MHC, delivered by nurses.

One hundred and twenty-three patients were randomly assigned to either guided self–instruction (*n* = 61). Randomisation was computer generated, with allocation by numbered sealed envelopes. Group allocation was open to all those involved. Patients fulfilled US Centers for Disease Control and Prevention (CDC) criteria for CFS. Primary outcome variables were fatigue severity and physical and social functioning, measured with the Checklist Individual Strength (CIS) and the Medical Outcomes Survey Short Form-36 (SF-36) respectively.

After six months, patients who followed guided self-instruction reported a significantly larger decrease in fatigue compared to the waiting list (mean difference -8.1 95% confidence interval (CI) -3.8 to -12.4, controlled effect size 0.70). There was no significant difference in physical and social functioning. However, post-hoc analyses showed a significant decrease in fatigue and physical disabilities following the intervention in a subgroup of patients with physical disabilities at baseline (SF-36 physical functioning ≤70).

Implementation of guided self-instruction in a community-based MHC was partially successful. The minimal intervention can be effectively implemented for CFS patients with physical impairments.

Introduction

Patients with chronic fatigue syndrome (CFS) have severe fatigue lasting longer than six months. The fatigue is not the result of a known organic disease or ongoing exertion, not alleviated by rest and leads to substantial functional impairment [1, 2]. Several systematic reviews and controlled trials have shown that cognitive behaviour therapy (CBT) leads to a significant reduction in symptoms and disabilities in patients with CFS [3-5]. CBT is aimed at cognitions and behaviours assumed to perpetuate the fatigue. It is a safe treatment and a subgroup of patients fully recovers [5-7].

CBT for CFS is an intensive treatment, with 13-16 sessions depending on the protocol used [8-11]. There is evidence that not all patients need such intensive treatment. Knoop et al. [12] showed, in a randomised controlled trial (RCT), that a minimal intervention for CFS, guided self-instruction, leads to a significant decrease in fatigue and disabilities. For a subgroup of patients, the minimal intervention sufficed. If the minimal intervention was not successful, patients needed substantially fewer sessions of additional CBT, compared to patients who were referred directly for regular CBT [13]. The minimal intervention consisted of a booklet with instructions, based on the protocol of CBT for CFS, and two-weekly email contact with a therapist.

Guided self-instruction was delivered at a tertiary university hospital with guidance of qualified cognitive behavioural therapists, who had extensive experience in treating patients with CBT for CFS. In the Netherlands, there is a lack of treatment capacity for patients with CFS [14]. To increase treatment capacity it is necessary to offer evidence-based treatments for CFS outside specialised treatment settings. The objective of this study was to test whether the minimal intervention was also effective when delivered at a community-based mental health centre (MHC). An MHC in the southwest of the Netherlands was chosen as the clinical practice setting. This centre had not previously treated CFS patients. Psychiatric nurses, novices with respect to CBT and the treatment of CFS, were trained to deliver the minimal intervention.

Method

Patients

Patients could participate in the study (NTR1223) if they had been referred by a general practitioner (GP) or consultant to GGZ WNB, a Dutch regional community-based MHC in the southwest of the Netherlands, and were diagnosed as having CFS according to the US Centers for Disease Control and Prevention (CDC) criteria [1, 2]. All referred patients, aged between 18 and 65, received a baseline assessment. In accordance with the CDC

criteria for CFS, patients were eligible to enter the study if they (1) were severely fatigued, operationalised as scoring ≥35 on the subscale Fatigue Severity of the Checklist Individual Strength (CIS) [15], (2) were fatigued for six months or longer, (3) were severely disabled, operationalised as scoring ≤70 on the subscale Physical and/or Social Functioning of the Medical Outcomes Survey Short Form-36 (SF-36) [16], and (4) reported at least four out of eight additional symptoms; unrefreshing sleep, post-exertional malaise, headache, muscle pain, multi-joint pain, sore throat, tender lymph nodes and impairment of concentration or memory [1, 2]. The assumption was made that the referring GP or consultant excluded the presence of somatic diseases or psychiatric disorders and the use of medication that could explain the fatigue.

Design and procedures

The study was an RCT in which the minimal intervention was compared to a waiting list. The ethics committee of the Radboud University Nijmegen Medical Centre approved the study. Referred patients were contacted by telephone to ascertain that they understood they were being referred for a study investigating the effectiveness of a minimal intervention for CFS. Patients who were willing to participate were given verbal information and sent written information about the study. After written informed consent was obtained, patients were requested to complete a set of questionnaires to assess fatigue severity, duration of the fatigue, number of CDC symptoms and level of disabilities, and also to gain information on medication use and self-reported level of psychopathology, including depressive symptoms. If the diagnosis of CFS was doubtful, based on this assessment and/or the referral letter, a CFS expert contacted the referring GP or consultant for additional information to evaluate whether the diagnosis CFS was justified. Eligibility was examined again during the 30-min intake session with the psychiatric nurse, who asked the patient about the presence of somatic or psychiatric conditions other than CFS. If they were present, the nurse contacted the researcher who informed the CFS expert. If necessary, the expert contacted the GP or consultant for additional information. If the diagnosis of CFS could be confirmed, the patient was included in the study. Furthermore, psychiatric nurses were instructed to temporarily exclude patients who were engaged in a legal procedure concerning disability related financial benefits. This was done because a previous intervention study had shown that being engaged in such a procedure predicted a negative treatment outcome [17]. During the intake session, the nurse who coached the patient during the minimal intervention explained the goals of guided self-instruction to the patient. Randomisation took place at the end of the session. If a patient was assigned to guided self-introduction, they were advised to stop other treatments for fatigue [8].

To ensure concealed allocation, a statistical advisor, independent of the study, prepared numbered and sealed envelopes by coding them according to a computer-generated list of random numbers. Randomisation was performed in blocks of six. During the intake session, in the presence of the patient, the psychiatric nurse telephoned the researcher, who opened the next envelope and stated the condition to which the patient had been assigned. The name of the patient was written on the envelope before it was opened, to prevent resealing and reusing. Group allocation was open to all those involved. Patients who were allocated to the waiting list received the minimal intervention after a delay of six months. Patients in both conditions were assessed at baseline and directly following the waiting period or intervention. If patients were not willing to fill in all of the questionnaires at the second assessment, they were asked to complete only the two questionnaires assessing the primary outcome variables.

Intervention

The guided self-instruction consisted of a booklet (58 pages) with information about CFS and assignments [12]. Patients could follow the programme, described in the booklet, week by week. The intervention was based on the protocol of CBT for CFS and took at least 20 weeks [18].

The first chapter in the booklet challenges patients to establish the goals of the therapy. In the following chapters the precipitating (triggering) and perpetuating (maintaining) factors are explained and individualised. Fatigue-related cognitions are challenged and patients are encouraged to develop a sense of control over their symptoms. In the third chapter patients learn to reduce the focus on fatigue. Subsequently, the patients establish a sleep routine as described in chapter 4. Chapter 5 explains to patients that there are two different physical activity patterns: a relative-active and a low-active activity pattern. Relatively active patients, characterised by an alternation of periods of (over)activity and periods of rest, first have to learn to divide their activities more evenly (chapter 6). Then they gradually increase their physical activity level, by walking or riding a bicycle. Patients with a low-active physical activity pattern start immediately with gradually increasing their physical activity level (chapter 7). In chapter 8, beliefs that activity would exacerbate symptoms are challenged. Chapter 9 invites patients to make a plan for work resumption. This plan contains the date when a patient will resume work, and how the patients will increase the number of hours worked. The next module is directed at modifying the patients excessive expectations regarding the response of their social environment to their symptoms. Often patients experience a lack of understanding from others. Patients learn how to communicate about CFS. In chapters 11 and 12 patients gradually increase their mental and social activities.

In chapter 13, patients attain the goals as formulated in chapter 1 step by step, including resumption of work. Finally, in the last two chapters, patients learn how to prevent a relapse and how to further improve self-control.

The booklet was sent to the patients after randomisation. During the intake session, the patients who were assigned to the intervention were asked to email once every two weeks. This enabled patients to ask questions about the treatment and nurses to monitor the progress patients made. If a patient did not email every two weeks, the nurse sent a reminder. The intervention was carried out by eight psychiatric nurses. They were trained in coaching patients with the minimal intervention in four training sessions of 4 h, in which they practised writing replies to emails. After the training, the nurses were given a test to evaluate their skills. This test, passed by all nurses, consisted of writing replies to emails of fictitious patients. The nurses received 2-weekly supervision by a cognitive behavioural therapist experienced in CBT for CFS.

The minimal intervention is adapted for two levels of physical activity: a relative-active and a low- active pattern of activity [19]. Activity patterns are usually assessed with an actometer, a small device worn around the ankle, and activity levels are assessed over a period of 12 days. However, as this was an implementation study, actometers were not available because of the high costs involved. Instead, the Physical Activity Questionnaire (PAQ) was used to gain an insight into the physical patterns [20]. Using a regression analysis in a group of 120 CFS patients, for whom both PAQ and actometer scores were available, the parameters were obtained for a formula that predicted the patients' activity patterns assessed with the actometer using the PAQ. The optimum cut-off score for the PAQ was set at 0.75, for which a sensitivity of 74.0% and a specificity of 79.2% were reached. If patients did not agree with their assignment to one of the two conditions, they were free to switch.

Outcome measures

The questionnaires were given at baseline and post-treatment or after the waiting list (six months after baseline assessment). The primary end-points were fatigue severity and disabilities. Psychological distress was a secondary end-point.

Fatigue. Fatigue was measured with the Fatigue Severity subscale of the CIS. This subscale assesses fatigue severity over the past two-week period. The questionnaire consists of eight items that have to be answered on a seven-point scale, with scores ranging from 8 (no fatigue) to 56 (severe fatigue). Reference values for healthy Dutch subjects are 17.3 ± 10.1 [21]. The CIS has good internal consistency, and discriminative validity, and is sensitive to change detection [15].

Disabilities. The level of disabilities was assessed with the SF-36 subscales 'Physical Functioning' and 'Social Functioning'. These subscales measure the extent to which health interferes with a variety of activities. Scores on both subscales range from 0 (maximum limitations) to 100 (no limitations). Reference values for healthy Dutch subjects for physical and social disabilities are 83.0 ± 22.8 and 84.0 ±22.4 respectively [22]. The SF-36 is a reliable and valid instrument [16].

Psychological distress. This was assessed with the Brief Symptom Inventory (BSI) [23], which consists of 53 items scored on a five-point Likert scale. The BSI is a brief form of the Symptom Checklist 90 (SCL-90) [24]. The general severity index, which combines the number of symptoms and the intensity of the perceived distress brought on by the symptom, was used as an indicator of the current distress level.

Significant clinical improvement. To determine whether the changes in fatigue severity were clinical meaningful, a cut-off score for significant clinical improvement was used. Patients were regarded as significantly clinically improved with respect to fatigue if (1) the change in fatigue was statistically reliable (reliable change index >1.96) [25] and (2) the fatigue score at post-treatment was <35 on the CIS subscale Fatigue Severity. This latter score is within 2 standard deviations (*SD*) of the mean for healthy adults and below 2 SD of the mean for CFS patients [7].

Analysis

Power calculation showed that, to reach a clinical relevant change of 5.5 points on the subscale Fatigue Severity of the CIS, assuming a significance of 5%, a power of 85% and a drop-out rate of 20%, 60 patients were needed in each condition. Calculations were based on the results of the study testing the efficacy of guided self-instruction for CFS in a tertiary treatment facility [12].

Data analyses were performed using SPSS version 16.0 (SPSS Inc., USA) Independent-samples *t* tests and χ^2 tests were used to determine whether there were differences in the patient characteristics at baseline between the two conditions. Analyses of the treatment effect were performed using mixed models. Both baseline and second assessment measurements were used as dependent variable, and occasion (pre/post), condition (guided self-instruction/ waiting list) and an interaction variable of both were the independent variables. Because of randomisation we did not expect any differences at baseline between the two conditions. This made it possible to use the occasion by condition interaction to test the effect of the treatment. Two modelling alternatives were used. The more complex model allowed for a

correlation between measurements of the same subjects on the two occasions, together with different variances at baseline and after guided self-instruction or the waiting period. The simpler model assumes a heterogeneous compound symmetry structure for occasion, thus effectively assuming the post-treatment variances in both conditions to be equal.

Comparisons were performed on all observed data. Significance was assumed at p <0.017 in mixed model analyses (0.05 divided by 3, i.e. the number of primary outcome variables). Differences between the two conditions in the proportion of patients with a significant clinical improvement were examined with $\chi 2$ tests on the completers. Controlled effect sizes for fatigue severity, physical and social functioning were also calculated ((mean difference intervention - mean difference control group)/SD pooled) [26] for the completers and compared to the previous study [12]. A sensitivity analysis was undertaken to test the robustness of the results of the mixed model analysis. Missing values at post-treatment results were replaced by last observation carried forward (LOCF) method.

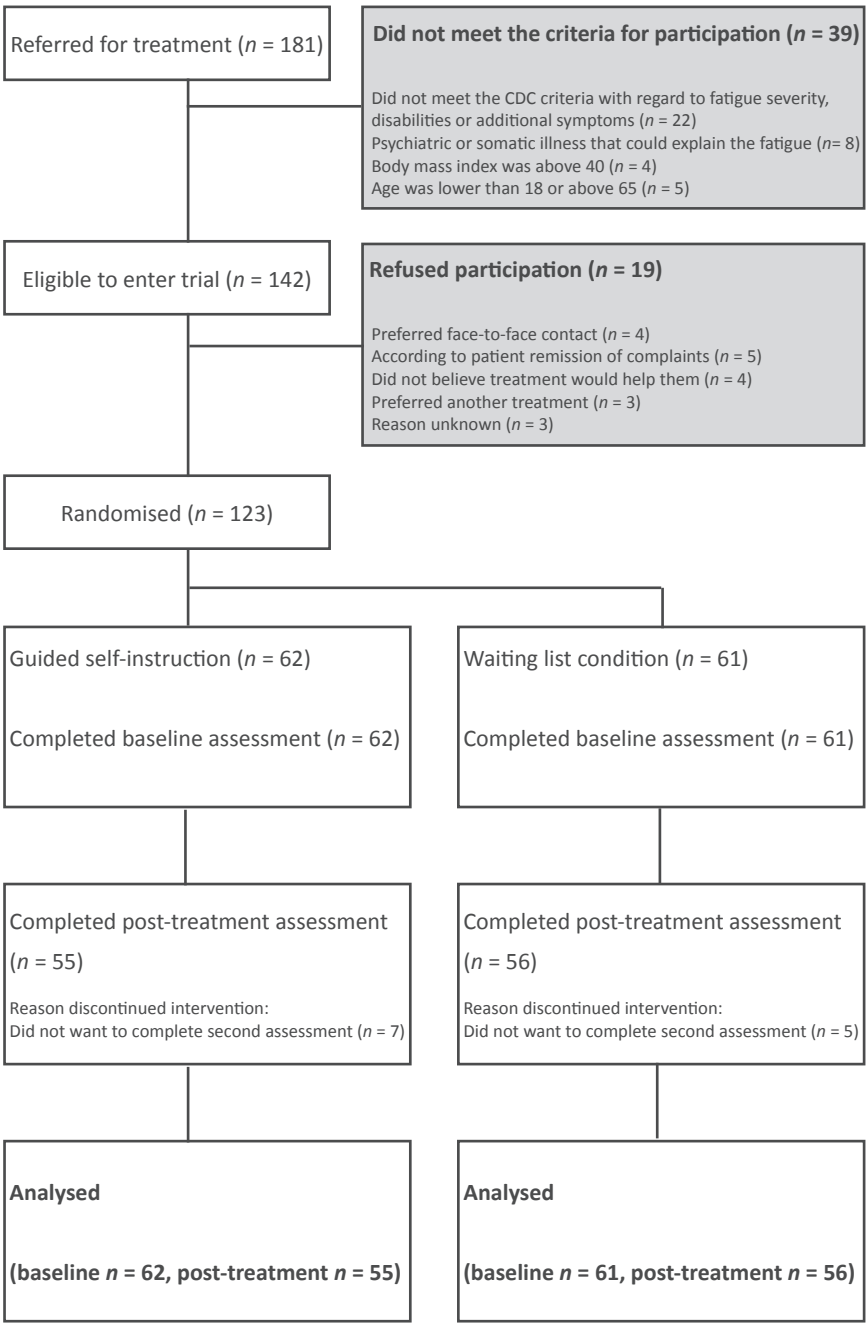
The inclusion criterion that a patient must have disabilities at the level of physical and/or social functioning meant that not all patients experienced disabilities in physical and social functioning. This meant that some patients could not show the expected increase in physical or social functioning following the minimal intervention as they had already scored within the non-disabled range (>70), leading to a reduction in statistical power for these outcome measures. Therefore post-hoc analyses were performed for the subgroups of patients who did experience disabilities in physical or social functioning. Analysis of the treatment effect using mixed models was repeated for the subgroup of patients who scored ≤70 on the subscale Physical Functioning, and the subgroup who scored ≤70 on the subscale Social Functioning. Significance was assumed at p <0.05 for all post-hoc analyses.

Results

Study population

Figure 1 shows the trial profile. Of the 181 patients referred between February 2008 and January 2010, 142 (78%) were eligible to enter the trial. Reasons for exclusion were failure to meet the inclusion criteria for CFS with regard to fatigue severity, disabilities and additional symptoms (22%), presence of psychiatric or somatic illness (4%), body mass index (BMI) >40 kg/m^2 (2%), and aged <18 or >65 years (3%). Nineteen patients (13%, 19/142) refused to take part in the study because they preferred face-to-face contact, experienced remission of complaints, had no faith in treatment or preferred another treatment. For three patients the reason for refusal was unknown.

Figure 1. Flow of participants through the study



The remaining 123 patients were randomly assigned to guided self-instruction (*n* = 62) or the waiting list (*n* = 61). In the intervention condition, 55 (89%) patients had a complete assessment, including three patients who filled out the shortened post-treatment assessment. Fifty-six (92%) patients, including four patients who completed the abridged questionnaire, had complete data after the waiting period. Baseline characteristics showed no significant imbalances after randomisation (Table 1). During the study, for 12 patients the diagnosis CFS turned out to be incorrect: four patients had a possible somatic explanation for their fatigue (e.g. brain damage), and eight patients seemed to have a psychiatric co-morbidity, of whom two had a substance-related disorder. The 12 patients were equally distributed between the two conditions. None of these patients were excluded from analyses.

As the results (conclusions and confidence intervals) from the simpler model were identical to the results from the more complex model, the results from the simpler model are presented for all analyses.

Table 1. Baseline characteristics and comparison of guided self-instruction versus waiting list

Baseline characteristics	Guided self-instruction (*n* = 62)	Waiting list (*n* = 61)	*t*-value$_{(121)}$	*P*
Demography				
Age (years), mean (*SD*)	36.3 (12.1)	36.4 (13.6)	-0.38	0.97
Duration of the complaints (months), median (min - max)	48 (6 - 464)	60 (6 - 625)	-0.39	0.69
Gender (male/female)	16 /46	11 /50	χ^2 = 1.09	0.38
Outcome measures, mean (*SD*)				
Fatigue severity	51.0 (5.3)	51.6 (5.5)	-0.55	0.58
Physical functioning	50.0 (22.0)	51.6 (22.6)	-0.39	0.70
Social functioning	37.7 (22.3)	41.0 (21.7)	-0.83	0.41
Perpetuating factors				
Activity pattern (low-active/ relative-active)	24 /38	23 /38	χ^2 = 0.13	1.00

SD, Standard deviation.

Efficacy of the minimal intervention

The second assessment was planned six months after baseline assessment. However, not all patients returned the questionnaires immediately, resulting in variation in the time passed between the two assessments. There was no significant difference in the mean time passed from baseline to second assessment between the intervention condition (8.2 months, *SD* = 3.6) and the waiting list condition (7.4 months, *SD* = 3.5) (*t* = 1.23, *df* = 109, *p* = 0.16). In the intervention condition there was no significant correlation in the time passed between the two assessments and change in fatigue severity (r = 0.01, *p* = 0.48). During guided self-instruction the nurses sent a mean of 12.3 (*SD* = 5.4) emails per patient. Patients sent a mean number of 8.8 (*SD* = 5.4) emails. There was no significant correlation between the numbers emails sent by the patient and change in fatigue severity (*r* = - 0.12, *p* = 0.39).

Primary analyses were based on all observed data. Patients in the intervention condition reported a significantly greater decrease in fatigue severity. For the outcome measures physical functioning, social functioning and psychological distress, the contrast was not significantly different between the two conditions. Mean, standard deviation and confidence interval on the outcome variables are presented for completers (Table 2).

After guided self-instruction, 33% of the completers showed a significant clinical improvement in fatigue. This percentage was significantly larger compared to the waiting list condition (9%) (Table 3).

The controlled effect size was 0.70 for fatigue severity and 0.32 and 0.29 for physical functioning and social functioning respectively. The controlled effect sizes of the previous trial were 0.67 for fatigue and 0.40 for physical functioning [12]. The subscale social functioning was not reported in the study of Knoop et al. [12]

The results of the sensitivity analyses on the three primary outcome variables were not different from the mixed model analyses (data not shown).

Table 2. Change in outcome between baseline and post-treatment for the primary and secondary outcome variables

	Guided self-instruction		Waiting list			Results mixed models		
Outcome measure	Baseline (*n* = 62) mean (*SD*)	Second assessment (*n* = 55) mean (*SD*)	Baseline (*n* = 61) mean (*SD*)	Second assessment (*n* = 56) mean (*SD*)	Difference Mean (95% CI)	*df*	*F*	*p*
CIS fatigue severity	51.0 (5.3)	39.6 (14.1)	51.6 (5.5)	48.3 (8.1)	-8.1 (-3.8 to -12.4)	119.904	14.106	<0.01
SF-36 physical functioning	50.0 (22.0)	65.4 (24.9)	51.6 (22.6)	59.3 (22.9)	7.37 (-0.9 to 15.65)	113.957	3.114	0.08
SF-36 social functioning	37.7 (22.3)	53.2 (33.0)	41.0 (21.7)	49.3 (24.8)	7.81 (-3.24 to 18.86)	111.670	1.959	0.16
BSI psychological distress[a]	1.02 (0.64)	0.77 (0.68)	1.02 (0.61)	0.86 (0.55)	-0.10 (-0.2 to 0.09)	107.665	1.100	0.30

CIS, Checklist Individual Strength; SF-36, Medical Outcomes Survey Short From-36; BSI, Brief Symptom Inventory; CI, confidence interval; *df*, degrees of freedom. [a] For the secondary outcome measure, psychological distress, only 52 patients completed post-treatment assessment in both conditions. The mean, standard deviation (*SD*) and confidence interval (CI) on the outcome variables at second assessment are presented for the completers. The results of the mixed models are based on all observed data.

Post-hoc analyses

Table 4 shows the data from the post-hoc analyses for patients with a score of ≤70 on the subscale Physical Functioning at baseline (guided self-instruction n = 53, waiting list n = 50). There was a significant difference between the minimal intervention and the waiting list for fatigue severity and physical functioning. There was no significant difference in social functioning. In the subgroup of patients with a score of ≤70 on the subscale Social Functioning (guided self-instruction n = 58, waiting list n = 55) a significant difference was found in fatigue severity between the two conditions (F ratio = 13.728, df = 109.705, p <0.01). There were no significant differences in physical and social functioning (respectively, F ratio = 2.505, df = 104.726, p >0.05 and F ratio = 1.248, df = 101.223, p >0.05).

Discussion

The aim of this study was to evaluate whether guided self-instruction, a minimal intervention for CFS carried out by psychiatric nurses, was effective when implemented in an MHC. The results showed a significant reduction in fatigue after the intervention compared to the waiting list. Significantly more patients reported a significant clinical improvement in fatigue following guided self-instruction. No significant differences were found on the other two primary outcome variables, physical functioning and social functioning, although there was a trend in the favour of the intervention. The level of psychological distress was not significantly different between the two conditions at second assessment. Controlled effect sizes for fatigue severity and physical functioning were similar to those in the previous trial testing the effectiveness of guided self-instruction for CFS [12]. A significant reduction in fatigue and physical functioning was found in the subgroup of patients who reported substantial impairments in physical functioning at baseline. We conclude from these data that implementation of guided self-instruction in an MHC was partially successful. It does lead to a reduction in fatigue, and in the subgroup of patients with physical disabilities, physical functioning also improves significantly. The criterion that patients with CFS must report impairments in physical functioning is often applied in studies testing the efficacy of behavioural interventions [4, 5, 10]. The results of this study justify a broader implementation of guided self-instruction for those CFS patients who report impairments in physical functioning.

Following the intervention, one third of the patients reported significant clinical improvement in fatigue. This is less than the 48% reported by CFS patients after regular face-to-face CBT [13]. Guided self-instruction could form the first step in stepped care for CFS, followed by additional CBT, if desirable. It has been shown that patients can profit from CBT after the minimal intervention. In the same study it was found that treatment outcome for stepped care, guided self-instruction, if necessary followed by additional CBT, is not inferior to the outcome of regular CBT [13].

Table 3. Comparison of proportion of significant clinical improvement in CIS fatigue severity

Outcome measure	Guided self-instruction (*n* = 55)	Waiting list (*n* = 56)	OR (95% CI)	χ^2
CIS fatigue severity, proportion (%)	18/55 (33)	5/56 (9)	5.0 (1.69-14.57)	<0.01

CIS, Checklist Individual Strength; OR, odds ratio; CI, confidence interval.

Table 4. Change in outcome between baseline and post-treatment for the subgroup SF-36 physical functioning is ≤70 at baseline

	Guided self-instruction		Waiting list		Results mixed models			
Outcome measure	Baseline (*n* = 53) mean (*SD*)	Second assessment (*n* = 46) mean (*SD*)	Baseline (*n* = 50) mean (*SD*)	Second assessment (*n* = 46) mean (*SD*)	Difference Mean (95% CI)	*df*	*F*	*p*
CIS fatigue severity	51.3 (5.1)	38.9 (14.3)	52.5 (4.8)	50.1 (6.2)	-9.9 (-5.4 to -14.3)	99.830	19.389	<0.01
SF-36 physical functioning	44.5 (18.7)	63.0 (25.9)	43.8 (16.3)	53.4 (18.7)	9.05 (0.2 - 17.9)	92.714	4.135	<0.05
SF-36 social functioning	38.0 (22.9)	53.0 (34.3)	40.0 (23.1)	45.7 (24.2)	10.05 (-2.5 to 22.6)	92.725	2.548	0.11

CIS, Checklist Individual Strength; SF-36, Medical Outcomes Survey Short From-36; BSI, Brief Symptom Inventory; CI, confidence interval; *df* degrees of freedom.

Besides impairments in physical functioning, patients with CFS also report impairments in other domains of functioning. In the previous RCT testing the efficacy of guided self-instruction [12], the Sickness Impact Profile (SIP) [27] was used to assess disabilities in all domains of functioning. The disabilities were found to decrease significantly following the intervention. However, because of the duration of the SIP and its complex scoring method, it was less suitable for this implementation study. We therefore decided to use the subscale Social Functioning of the SF-36 [16], a questionnaire that is easy to administer and score, and comprises only two questions. It is conceivable that the SF-36 Social Functioning has limited sensitivity to detect change. To our knowledge, the sensitivity of this subscale to change has never been demonstrated in CFS patients. A recent study showed that the Work and Social Adjustment Scale is a reliable and valid assessment tool for measuring disabilities in work and social functioning in patients with CFS [28]. The instrument is also short but sensitive to detecting change brought about by CBT, which makes it suitable for use outside specialised treatment centres. Further research is needed to determine whether not finding significant treatments effects on domains of functioning other than physical functioning is caused by the limited sensitivity of the instrument used or by a reduced efficacy when implementing the intervention outside a specialised treatment setting.

Implementation of behavioural interventions for patients with CFS outside specialised treatment settings is not always successful. Scheeres et al. showed that CBT for CFS can be effective in a community-based MHC. Effect sizes for fatigue severity and physical functioning were similar to those of previous RCTs testing the effectiveness of CBT for CFS [10]. However, a recent implementation study found that the effectiveness of CBT for CFS differed significantly between MHCs (Wiborg et al. unpublished data). A study implementing pragmatic rehabilitation for CFS in primary care showed that fatigue decreased, but no significant effects were found for physical functioning [29]. A previous hospital-based trial had shown that the same treatment lead to a reduction in both fatigue and physical disabilities [30]. More research is needed to determine how implementation of behavioural interventions outside specialised treatment settings can be optimised.

By offering guided self-instruction in an MHC, instead of in a tertiary treatment centre, it might be assumed that patients would be referred in an earlier stage of their condition. The duration of illness of the CFS patients included in this trial was indeed shorter than that found in the previous study (median duration of complaints was 72 months versus 48 months in the present study) [12]. This suggests that implementation of the minimal intervention results in earlier treatment for CFS patients. However, the median symptom duration is still 48 months, which is long considering that CFS can be diagnosed when patients are severely fatigued for six months. By diagnosing CFS in an earlier stage, the suffering of the patient

could be reduced, as could the societal and medical costs of the illness. With regard to age, fatigue severity and level of disabilities the patients who participated in the present study did not differ from the patients in the previous trial [12].

This study has some limitations. First, patients could only participate if they fulfilled the operational criteria for CFS. This was assessed on the basis of the referral letter of the GP or consultant, the questionnaires at baseline, and the intake session with the psychiatric nurse. It has been shown that diagnosing CFS on the basis of clinical assessment by a non-CFS specialist can lead to misclassification [31]. In our trial we tried to limit misclassifications, (1) by instructing the referring GPs and consultants with brochures, information letters and small group sessions on how to diagnose CFS according to the CDC criteria, (2) by using relevant questionnaires to check if a patient fulfilled the CDC criteria for CFS and (3) by an intake session with the psychiatric nurse, who asked patients if somatic or psychiatric conditions were present. However, during the trial we had to conclude that 12 patients had psychiatric or medical co-morbidities that could explain the presence of fatigue according to the CDC criteria [1, 2]. This became clear during supervision or at the second assessment of patients from the waiting list. In all cases the misclassifications was ascertained by the psychiatric nurse, who had an final interview with the patient at the second assessment, or by a psychologist, who performed an additional assessment. A standardised medical and psychiatric assessment probably would have reduced the number of misclassifications. However, such an assessment is difficult to conduct as part of clinical routine. Because this was an implementation study, we deliberately chose a less stringent procedure. Patients who were wrongfully included in this study were not excluded from data analyses, as the effects of the misclassifications on outcome were considered to be a consequence of the chosen implementation strategy.

Second, assessment of the physical activity patterns of patients was not based on actometer scores, a valid an reliable method to determine the activity pattern [19]. In the current study a relatively new questionnaire was used to assess the physical activity patterns. When using an actometer, the proportion of relatively active patients is about 75%. In the current study, about 60% of the patients had a relatively active physical activity pattern. Inaccurate allocation to one of the two treatment protocols could have influenced the treatment results.

Third, treatment adherence or treatment dose was not assessed. Patients were asked to email once every two weeks about the progress made. The researcher received a copy of all emails sent by the nurses and patients. The number of emails sent by the patient does not give specific information about treatment adherence. Patients were free to decide what

they emailed to the therapist, making it difficult to determine adherence form the content of the email. As the emails were discussed in the two-weekly supervision, it was possible to check if the answers of the psychiatric nurse were in accordance with the treatment protocol. In the previous study testing the efficacy of guided self-instruction, there was no relation between the number of emails sent by the patient and fatigue severity at the second assessment [32]. Guided self-instruction is a self-paced treatment, which makes it difficult to assess treatment adherence and the dose of treatment received. This is inherent to this type of self-management intervention, where the therapist does not set the pace of the intervention.

Fourth, there are no follow-up data available. As a result, we do not know if the effects of the intervention sustained once treatment had ended.

This study demonstrated that, after training, less-qualified mental health-care workers, without any prior experience in treating CFS patients were able to coach patients during guided self-instruction. There was considerable variability in treatment results between the nurses. The range in clinically significant improvement in fatigue was 17-44% (the nurse who treated only one patient, was not taken into account). Because of the limited number of participating nurses and the relatively small number of treated patients per therapist (range 5 - 11), it was not possible to test for differences in success rates between therapists. This is a shortcoming of the study.

Finally, for implementation of guided self-instruction in an MHC, it is also important to have information about costs and benefits of the treatment for individual patients, the health-care system and society. We did not perform such an analysis. An uncontrolled study [33] established that implementing CBT for CFS in an MHC has a favourable cost outcome ratio from a societal perspective. From a health-care perspective, the outcome of the ratio depended on the value assigned to a clinically significant improvement of CFS.

To conclude, the results of this study suggest that guided self-instruction for CFS, delivered by psychiatric nurses, can be implemented successfully in an MHC for CFS patients with substantial physical disabilities. This increases the prospects of implementation of evidence-based treatments for CFS. Wider implementation of the minimal intervention, preferably in the context of stepped care, would be a logical next step.

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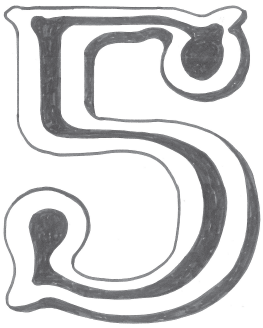

Moderators of the treatment response to guided self-instruction for chronic fatigue syndrome

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Abstract

The efficiency and efficacy of guided self-instruction for chronic fatigue syndrome (CFS) can be enhanced if it is known which patients will benefit from the intervention. This study aimed to identify moderators of treatment response.

This study is a secondary analysis of two randomised controlled trials evaluating the efficacy of guided self-instruction for CFS. A sample of 261 patients fulfilling US Center for Disease Control and Prevention criteria for CFS was randomly allocated to guided self-instruction or a wait list. The following potential treatment moderators were selected from the literature: age, fatigue severity, level of physical functioning, pain, level of depressive symptoms, self-efficacy with respect to fatigue, somatic attributions, avoidance of activity, and focus on bodily symptoms. Logistic and linear regression analyses were used with interaction term between treatment response and the potential moderator.

Age, level of depression, and avoidance of activity moderated the response to guided self-instruction. Patients who were young, had low levels of depressive symptoms, and who had a low tendency to avoid activity benefited more from the intervention than older patients and patients with high levels of depressive symptoms and a strong tendency to avoid activity.

Guided self-instruction is exclusively aimed at cognitions and behaviours that perpetuate fatigue. Patients with severe depressive symptom may need more specific interventions aimed at the reduction of depressive symptoms to profit from the intervention. Therefore we suggest that patients with substantial depressive symptoms be directly referred to regular cognitive behaviour therapy.

Introduction

Chronic fatigue syndrome (CFS) is characterised by medically unexplained, prolonged and disabling fatigue. According to the widely used consensus criteria of the US Center for Disease Control, there have to be at least four of the following eight additional symptoms present for the CFS diagnoses to be warranted: sleep that does not alleviate fatigue, post-exertion malaise, headaches, muscle pain, multi-joint pain, sore throat, tender lymph nodes, and impaired concentration or memory [1]. Cognitive behaviour therapy (CBT) is directed at changing cognitions and behaviours that perpetuate fatigue [2] and has been shown to be effective in reducing fatigue and disabilities in patients with CFS [3, 4]. However, CBT for CFS is only effective after 13 - 16 sessions [5-8]. As not all patients need such intensive treatment, a self-guided intervention has been developed [9], based on the protocol of CBT for CFS. Instead of face-to-face sessions, patients go through a self-help booklet with assignments, at their own pace and with email guidance from a therapist.

Two randomised controlled trials (RCTs) evaluated the effectiveness of guided self-instruction for CFS compared to patients with CFS on a wait list [9, 10]. The first RCT was performed in a tertiary treatment centre. Cognitive behavioural therapists who had extensive experience in treating patients with CBT for CFS carried out the intervention [9]. In the second RCT, psychiatric nurses in a community-based mental health-care centre (MHC) were trained to deliver the guided self-instruction. Before the start of the study the psychiatric nurses were unacquainted with CBT and the treatment of CFS [10]. In both trials patients who followed the minimal intervention reported a significant reduction in fatigue [9, 10]. However, the minimal intervention sufficed for only a subgroup of the patients. Patients who did not profit from the minimal intervention were referred to additional CBT. It has been shown that patients can profit from additional CBT if the minimal intervention is unsuccessful [11].

Stepped care for CFS, consisting of guided self-instruction and followed by additional CBT if needed, offers the opportunity to make the treatment of CFS more efficient. Efficiency can be further enhanced if patients who are likely to profit from the minimal intervention can be identified. Identifying moderators is a way to understand the variability of outcomes in psychosocial interventions. Knowing moderators of guided self-instruction will inform which patients are likely to benefit from the intervention. It has already been shown that patients with an extremely high level of disabilities profit less from the minimal intervention compared to those without severe disabilities [9]. These patients may have better treatment outcomes with regular CBT than with the minimal intervention.

Studies that investigated moderators and predictors of treatment outcome in face-to-face CBT for CFS were reviewed. These studies show that focusing on bodily symptoms

and attributing symptoms to a physical cause are related to poor treatment outcomes [12, 13]. However, evidence concerning the latter is contradictory [6, 13, 14]. Additionally, patients with a high sense of control with respect to fatigue gain greater benefit from CBT than those with a low sense of control [6] and patients with a low activity pattern tend to show less improvement following CBT compared to those with a high activity pattern [6]. After adapting the treatment manual of CBT for CFS, the relation between the level of physical activity and treatment outcome was no longer present [15]. Good CBT treatment outcomes are associated with a change in avoidance of activity and related beliefs [16]. The prognostic role of depression is still unclear. Some studies found that depression was negatively related to treatment outcomes, whereas others found no relation [17-19]. A recently published study found that baseline levels of depressive symptoms, measured with the HADS, significantly moderated fatigue at one-year follow-up in an behavioural minimal intervention for CFS [20]. In contrast with these findings Prins et al. [18] found that patients with depression and psychological distress benefited from CBT as much as others. There is also evidence to suggest that high levels of pain are negatively correlated with treatment outcome [21]. In addition, treatment seems to be less successful when patients are older, are members of a self-help group, are involved in a legal procedure concerning disability related benefits, or received a disablement insurance benefit [6, 7, 17].

This study investigated whether factors that are related to treatment outcome in CBT, are moderators of response to guided self-instruction on fatigue. Most studies use the continuous post-treatment score in fatigue as a dependent variable to gain insight in predictors or moderators of treatment outcome instead of significant clinical improvement in fatigue. However, the latter is clinically more meaningful. Therefore, in post-hoc analyses we aimed to identify moderators of post-treatment fatigue (continuous) and significant clinical improvement in fatigue (dichotomous) following guided self-instruction. Analysis were adjusted for baseline levels of fatigue.

Method

This study is a secondary analysis of data obtained in two RCTs (NTR570 and NTR1223) that tested the effectiveness of guided self-instruction for CFS compared with people with CFS who were on a wait list. Patients doing the guided self-instruction went through a booklet with assignments. They did this at their own pace, and they had email contact with a therapist. Patients on the wait list received CBT or the minimal intervention after a delay of six months. Both trials showed that after guided self-instruction significantly more patients reported a significant clinical improvement in fatigue. Patients were regarded significantly clinically improved with respect to fatigue if (1) the change in fatigue was statistically reliable (reliable change index >1.96) [22] and (2) the fatigue score at post-treatment was

<35 on the Checklist Individual Strength (CIS) subscale Fatigue Severity [23]. The other main findings of both RCTs are published elsewhere [9, 10]. To explore moderators of treatment outcomes of guided self-instruction, we re-analysed data from the two RCTs. After baseline assessment, patients were randomly assigned to either the minimal intervention or a wait list. Assessment took place prior and subsequent to treatment or placement on a wait list.

Samples

Participants were 261 patients meeting Center for Disease Control (CDC) criteria for CFS [1]. The ethic committee of the Radboud University Nijmegen Medical Centre approved of both studies, and written informed consent was obtained from all patients. The first RCT tested the efficacy of guided self-instruction in a tertiary treatment centre [9]. Patients were 18 years or older and able to speak and read Dutch. A medical and psychiatric evaluation was performed to exclude other causes of fatigue. All patients were severely fatigued (CIS, subscale Fatigue Severity ≥35), and severely disabled (Sickness Impact Profile (SIP), total score ≥ 700) [23, 24]. In total 169 patients were randomly assigned to either guided self-instruction or a wait list. During guided self-instruction, qualified cognitive behavioural therapists gave patients feedback on their assignments. In total ten patients (guided self-instruction n = 6, wait list n = 4) did not complete second assessment. Complete data were available for 78 patients following the intervention, and for 81 patients after the wait period.

The second RCT was delivered by psychiatric nurses in a community-based MHC [10]. All patients, aged between 18 and 65, were severely fatigued (CIS, subscale Fatigue Severity ≥ 35) for at least six months and reported physical and/or social disabilities in daily functioning (Medical Outcomes Survey Short Form-36 (SF-36), subscale Physical and/or Social Functioning ≤ 70) [23, 25]. Initially, 123 patients were randomly assigned, to either guided self-instruction (n = 62) or a wait list (n = 61). Seven patients following guided self-instruction and five patients of the waiting list did want to complete second assessment. Twelve patients (six patients of the intervention condition and six patients of the wait list) were excluded from analysis because of medical or psychiatric co-morbidity that could explain the fatigue. Misclassifications were confirmed by the nurse in attendance. Seven of the patients receiving a wrong diagnosis, did not also complete the second assessment. As a result, 52 patients included in the intervention had a complete assessment, and 50 patients after the wait period.

Design

Based on the existing literature of moderators and predictors of treatment outcome of CBT for CFS, the following variables were selected; age, fatigue severity, level of physical functioning, impact of pain, level of depressive symptoms, self-efficacy with respect

to fatigue, somatic attributions, avoidance of activity, and focus on bodily symptoms. Information on participants being members of a self-help group, if they were involved in a legal procedure concerning disability related benefits, or if they had received disablement insurance was unavailable.

Assessments

Sociodemographic characteristics

Gender, age, level of education, and civil status of participants were noted.

CFS symptoms

Fatigue. The subscale Fatigue Severity of the CIS was used to measure the experienced fatigue over the past two-week period prior to testing [23]. This subscale consists of eight items, each scored on a seven-point Likert scale. High scores indicate a high level of fatigue. A commonly used cut-off score for fatigue severity is 35 (or higher). This score is two standard deviations above the mean of healthy controls. The CIS is a reliable and valid instrument for assessing fatigue in CFS [23, 26].

Pain. Pain was measured with the Bodily Pain subscale of the SF-36 [25]. This subscale consists of two items to measure the impact of pain and pain interference (i.e. how much pain limits the patient's daily functioning). The SF-36 Bodily Pain subscale provides a score range between 0 (worst) to 100 (best) with respect to pain.

Physical functioning. Disabilities were measured with the subscale Physical Functioning of the SF-36 [25]. On this subscale patients have to indicate if their health status limits them in specific activities such as walking, climbing stairs and carrying groceries. Scores range from 0 (maximum limitations) to 100 (no limitations). The SF-36 is a reliable and valid instrument [8, 25].

Depression

The Brief Depression Inventory for Primary Care (BDI-PC), a short screening questionnaire consisting of seven items of the BDI-II, was used to assess depressive symptoms [27]. The BDI-PC measures depression independent of physical symptoms such as fatigue. Each item can be rated on a 4-point scale (0-3). If the continuous BDI-PC score is a significant moderator, outcomes will be dichotomised in (1) clinical relevant depressive symptoms (BDI-PC ≥ 4) or (2) no clinical relevant depressive symptoms (BDI-PC ≤3) [28]. This will be done because the dichotomous measure can be interpreted as clinically depressed versus non-depressed. The BDI-PC has a high internal consistency (Chronbach α = .86) and displays convergent validity [27].

Perpetuating factors

Self-efficacy with respect to fatigue. To measure the patients' sense of control over their symptoms, the Self-Efficacy Scale (SES-28) was used [2]. This scale consists of seven items, which is scored on a four-point Likert scale. The score ranges from 7 to 28 with a high score indicating a high sense of control. The internal-consistency of the SES-28 is good [2].

Somatic attributions. Somatic attributions with respect to CFS were measured by the causal attribution list. The list consists of five possible physical causes of fatigue that have to be scored on a four-point Likert-scale. Two examples of the questions are: 'Do you think your complaints started because there is physically something wrong with you?' and 'Do you think your complaints have to do with your immune system?'. The total score ranges from 5 to 20, with a high score indicating a strong somatic attribution. Cronbach's alpha reliability is 0.74 [6].

Avoidance of activity. Five expressions of avoidance of activity were selected. The patient was asked if she or he (1) avoids symptoms by avoiding strenuous activity, (2) stops with activities in case of pain or when feeling fatigued, (3) restricts him or herself to simple activities, (4) takes a rest by sitting or lying down in case of pain or when feeling fatigued and (5) tries to take as much rest as possible to avoid symptoms. All items were scored on a four-point Likert scale. A high sum was indicative of a high tendency to avoid activity [23, 29]. The Cronbach's alpha reliability coefficient in this study is 0.80.

Focus on bodily symptoms. The Illness Management Questionnaire Factor III subscale was used to measure symptom focus [30]. This questionnaire is specifically designed for CFS patients and has been shown to have good psychometric properties. It consists of nine items that measure the patient's approach to CFS in the last six months on a six-point Likert scale (ranging from 'never' to 'always'). The patient is asked about the preoccupation with symptoms and whether his life is dominated by CFS. Examples of the items are: 'I am constantly aware of how I am feeling' and 'I spend a lot of time thinking about my illness'. Unfortunately, data regarding the focus on bodily symptoms were not measured in the RCT performed in the tertiary treatment centre.

Analysis

Data analyses were performed using SPSS 16.0 (SPSS Inc., USA). Significance was assumed at $p < 0.05$ in all analyses. Both RCTs were not powered for moderator analysis but as intervention studies. Therefore, the moderator analyses have to be interpreted as exploratory post-hoc analyses. Analyses were adjusted for baseline levels of fatigue.

Independent sample *t*-tests were used to determine whether there were differences in potential moderator variables at baseline between the two conditions (intervention versus placement on a wait list condition). First, treatment effect was defined as the continuous post-treatment score in fatigue measured with the subscale Fatigue Severity of the CIS. To identify whether the selected variables moderated the effect of the intervention on fatigue at post-treatment assessment, linear regression analyses were used to test for significant interactions. Each potential moderator was centred so that the mean was set at zero. By centring variables, multicollinearity is reduced. In linear regression models we entered, the continuous post-treatment score as dependent variable, the intervention dummy (intervention condition = 1 versus control condition = 0), the centred potential moderator, the intervention by moderator interaction, and the centred continuous baseline fatigue score at baseline as independent variables. Furthermore, setting (tertiary treatment centre versus community-based MHC) and the interaction with intervention, moderator and centred continuous fatigue interaction, were entered as independent variables.

Second, to test the clinical relevance of our results, treatment effect-defined as significant clinical improvement in fatigue-was used as a dichotomous variable. Patients were regarded significantly clinically improved with respect to fatigue if (1) the change in fatigue was statistically reliable (reliable change index >1.96) [22] and (2) the fatigue score at post-treatment was <35 on the CIS subscale Fatigue Severity. This latter score is within 2 standard deviations (S.D.) of the mean for healthy adults and below 2 S.D. of the mean for CFS patients [31]. Logistic regression analyses were performed for each potential moderator. The significant clinical change (significant clinical improved = 0 versus not significant clinical improved = 1) was entered as dependent variable. The independent variables were similar as used when performing linear regression analyses.

Results

Baseline characteristics

Both groups (intervention versus wait list) were similar at baseline in terms of the potential moderator variables. There were no significant imbalances (Table 1).

Moderator analyses

Linear regression analyses showed three significant moderators by treatment effect, namely age (b = 0.15, p <0.05), level of depressive symptoms (b = 0.15, p = 0.04) and avoidance of activity (b = 0.17, p = 0.04) (Table 2). Young patients, patients with low levels of depression, and low tendency to avoid activity benefited more from the intervention than older patients and patients with high levels of depression and strong tendency to avoid activity.

If outcomes of depression are dichotomised, depression still moderated the response to guided self-instruction (b = 0.21, p = 0.02, 95% confidence interval (CI) 1.01, 11.45). This indicates that patients with clinically relevant depressive symptoms (score of 4 or above on the BDI-PC) have a small chance of a reduction in fatigue compared to non-depressed patients. No significant interactions were found for the other potential moderators; fatigue severity, level of physical functioning, impact of pain, self-efficacy with respect to fatigue, somatic attributions, and focus on bodily symptoms (Table 2).

Logistic regression analyses showed only two significant moderators: level of depressive symptoms (b = 1.40, p = 0.01) and avoidance of activity (b = 1.34, p = 0.03) (Table 3). Furthermore, there was a significant interaction between the dichotomised depression score and the minimal intervention (b = 5.00, p = 0.04, 95% CI 1.05, 23.80). Eighteen percent (9/51) of the patients with clinical relevant depressive symptoms, who followed guided self-instruction, reported significant clinical improvement in fatigue, compared to 11% (5/45) of the patients on the wait list. Of the patients with no clinical relevant depressive symptoms 40% (31/78) showed significant clinical improvement in fatigue following guided self-instruction compared to 6% (5/81) of the patients with no clinical relevant depressive patients on the wait list. Absence of clinically relevant depressive symptoms was related to significant clinical improvement in fatigue. In addition, patients with low avoidance of activity experienced more often significant clinical improvement following guided self-instruction compared to those with high avoidance of activity (Figure 1).

Figure 1: Chance of significant clinical improvement for the variable avoidance of activity

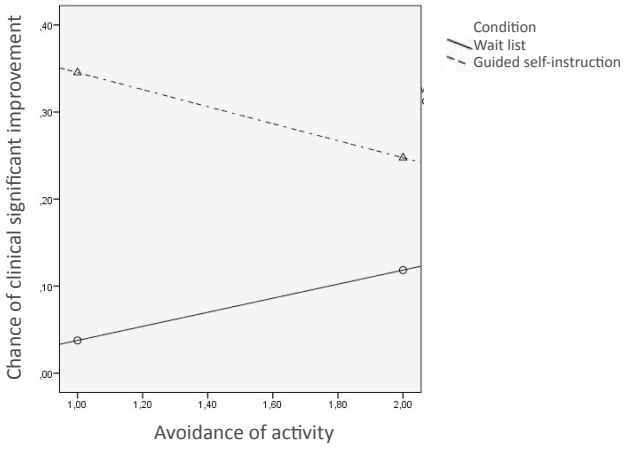

Table 1. Baseline comparison for potential moderator variables

	Guided self-instruction (*n* = 130)	Wait list (*n* = 131)
Sociodemographic characteristic, mean (SD)		
Age (years)	37.2 (10.9)	37.9 (12.1)
CFS symptoms, mean (SD)		
Fatigue	49.8 (5.3)	50.3 (5.7)
Physical functioning	51.7 (20.9)	53.6 (21.9)
Pain	53.0 (24.5)	53.9 (25.5)
Depression, mean (SD)		
	3.4 (2.6)	3.4 (2.9)
Perpetuating factors, mean (SD)		
Self-efficacy	17.3 (3.2)	17.2 (2.9)
Somatic attribution*	10.7 (3.0)	10.8 (3.1)
Avoidance of activity	11.9 (3.2)	11.9 (2.8)
Focus on bodily symptoms**	35.4 (9.3)	36.1 (7.1)

*For the outcome measures somatic attribution only 129 patients in the wait list condition had complete data. **For the outcome measure focus on bodily symptoms only data of the RCT performed in a community-based mental healthcare centre were available (guided self-instruction *n* = 52, wait list *n* = 50)

Table 2. Interaction tests for the potential moderators from linear regression models

	b	95% CI	*p*
Sociodemographic characteristic			
Age (years)	0.15	0.01, 0.45	<0.05
CFS symptoms			
Fatigue	-0.03	-0.56, 0.39	0.72
Physical functioning	0.11	-0.04, 0.21	0.17
Pain	0.00	-0.10, 0.10	0.99
Depression			
	0.15	0.04, 1.95	0.04
Perpetuating factors			
Self-efficacy	-0.06	-1.18, 0.56	0.48
Somatic attribution	0.10	-0.32, 1.43	0.21
Avoidance of activity	0.17	0.03, 1.78	0.04
Focus on bodily symptoms*	-0.02	-0.61, 0.52	0.88

CI, confidence interval *For the outcome measure focus on bodily symptoms only data of the RCT performed in a community-based mental healthcare centre were available, as a result setting and the accompanying interactions were not entered as independent variables in the linear regression analyses.

Table 3. Interaction tests for the potential moderators from logistic regression models

	b	95% CI	*p*
Sociodemographic characteristic			
Age (years)	1.06	0.99, 1.13	0.10
CFS symptoms			
Fatigue	0.95	0.84, 1.08	0.43
Physical functioning	1.04	1.00, 1.08	0.06
Pain	1.01	0.98, 1.04	0.77
Depression			
	1.40	1.08, 1.82	0.01
Perpetuating factors			
Self-efficacy	0.81	0.62, 1.05	0.11
Somatic attribution	1.13	0.87, 1.46	0.36
Avoidance of activity	1.34	1.03, 1.74	0.03
Focus on bodily symptoms*	1.02	0.87, 1.20	0.80

CI, confidence interval *For the outcome measure focus on bodily symptoms only data of the RCT performed in a community-based mental healthcare centre were available, as a result setting and the accompanying interactions were not entered as independent variables in the linear regression analyses.

Discussion

In this study we examined moderators of treatment outcome of guided self-instruction. Three moderators of treatment outcome were found. All moderators were independently related to treatment outcome. Age was found to be a significant moderator of treatment outcome when using linear regression analyses. Patients who were older benefited less from the intervention than young patients. The range of age was from 18 to 68 years. It was not possible to determine above what age immediate regular CBT is indicated. As logistic regression did not show age as a moderator, higher age may not be a good reason to exclude patients from guided self-instruction.

The presence of clinically relevant depressive symptoms was also found to moderate the response to guided self-instruction. Patients with severe depressive symptoms benefitted less from the intervention with respect to fatigue than those without severe depressive symptoms. Bentall et al. found the same in a minimal intervention: depressive symptoms predicted negative treatment outcomes [17]. Recently in the same type of intervention, Wearden et al. [20] also found that higher levels of depressive symptoms were associated

In a previous trial performed in a tertiary treatment centre, disabilities in different domains of functioning were associated with an unfavourable treatment response [9]. In this trial we chose to focus on disabilities in physical functioning, measured with the SF-36. The subscale Physical Functioning of the SF-36 measures disabilities in rather simple activities like carrying groceries, climbing stairs and walking [25]. The SIP measures disabilities in more complex activities such as work, social interactions, recreation and pastimes [24]. Physical functioning did not moderate treatment outcome. This is in contrast when disabilities are measured with the SIP. This finding implies that the SIP and the SF-36 not only measure different domains of functioning, but also that both questionnaires have a different relationship with the response to treatment, suggesting that it is important to operationalise the concept disabilities in different ways in CFS research.

Our study has several limitations. Both RCT's were designed to evaluate the effectiveness of guided self-instruction for CFS [9, 10]. As a result, data on some potential moderators of treatment outcome, as previously found in other studies, were not assessed. In addition, data regarding the focus on bodily symptoms were only available for the RCT performed in the mental health-care setting, which decreases the statistical power to identify moderators. Furthermore, we did not adjust the p-values for multiple testing. As this was an explorative study we chose not to correct for multiple testing. Replication of our study is necessary to confirm our results.

In conclusion, patients who show signs of avoidance of activity and patients with substantial depressive symptoms (BDI-PC ≥4) benefit less from guided self-instruction than patients with low tendency to avoid activity and those without severe depressive symptoms. Avoidance of activity has been suggested to be an important factor in the maintenance of CFS symptoms. Our results suggest that in a model of stepped care for CFS, patients with clinically relevant depressive symptoms may have better treatment outcomes if they are directly referred to CBT, as depressive symptoms do not seem to be a treatment moderator for regular CBT [18, 19]. Assessing patients' suitability for guided self-instruction is necessary for further development of a model of stepped care for CFS. By identifying moderators of treatment outcomes, variability of treatment outcome can be reduced, and treatment efficacy and efficiency enhanced.

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5

Implementing evidence-based practice for patients with chronic fatigue syndrome

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Abstract

The aim of our study was to explore whether community-based mental health care centres (MHCs) are able to implement and sustain cognitive behaviour therapy (CBT) for chronic fatigue syndrome (CFS) with the help of an implementation manual. We monitored the implementation process and treatment outcome data of three Dutch MHCs that implemented or sustained CBT for CFS, one in the context of a stepped care programme. We compared these data with findings of other treatment studies conducted in the context of CBT for CFS. All three MHCs included at least 40 patients with dropout rates between 15% and 35% from intention-to-treat to second assessment. Effect sizes ranged between 0.88 and 1.76 for changes in fatigue severity and 0.43 and 1.23 for changes in physical functioning. With one exception, these outcomes were within the range of our benchmark. Contrary to original expectations, we provided additional implementation support to the two MHCs new with CBT for CFS. We concluded that our implementation manual does not seem to substitute external support for team leaders and associated professions during initial implementation of CBT for CFS but may have the potential to make this assistance more efficient. Particular attention should be paid to challenges of implementing stepped care for CFS.

Introduction

Patients with chronic fatigue syndrome (CFS) suffer from medically unexplained and severely disabling fatigue that lasts for at least six months [1]. During the last two decades, cognitive behavioural therapy (CBT) for CFS has been developed and tested in specialised treatment settings [2-6]. In CBT for CFS, dysfunctional illness beliefs are usually challenged through a gradual increase in activity and cognitive restructuring techniques. This strategy is effective in reducing fatigue and disabilities in CFS patients [7-9].

Consequently, there is a growing interest in the dissemination of CBT for CFS outside specialised settings. For example, the Health Council of the Netherlands [10] urged to implement CBT for CFS on a large national scale to treat an estimated number of 30 000–40 000 Dutch CFS patients. It has been argued before that community-based mental health care centres (MHCs) are most suitable for implementation of CBT for CFS in the Netherlands [11]. In contrast to primary care practices or general hospitals, these settings usually employ cognitive behavioural therapists and have sufficient financial resources to invest in new specialised treatments. In addition, somatic attributions are less likely to be reinforced in mental health care settings.

Scheeres, Wensing, Knoop, and Bleijenberg [12] examined the specific requirements for successful implementation of CBT for CFS in a Dutch MHC. They found that therapists needed specific training and supervision in addition to the CBT for CFS manual in order to treat patients effectively. Also, referrers and patients had to be informed regularly about the new treatment options so that treatment capacities could be exploited adequately. In addition, an optimised patient flow, which included the avoidance of prolonged waiting periods, was necessary to reduce unexpectedly high dropout rates. A benchmark analysis showed that the effect sizes of the MHC were similar to the uncontrolled effect sizes of CBT for CFS in randomised controlled trials (RCTs) [12].

On the basis of this promising finding, Scheeres and Bleijenberg [13] wrote a manual in which they described their experiences with implementing CBT for CFS outside specialised settings. The main idea of this manual was that MHCs might be able to adopt CBT for CFS without additional help when they are adequately informed about the specific demands of the implementation. This could be of particular advantage for cost-efficient dissemination of evidence-based practice for CFS on a large scale. The aim of the present study was to examine whether three MHCs were able to implement and sustain CBT for CFS with the help of the implementation manual introduced by Scheeres et al. [13]. We evaluated implementation process and treatment outcome data of these MHCs.

Methods

Setting

Our study was conducted at three Dutch MHCs. One was located in an urban region in the west of the Netherlands. The two other MHCs were located in rural areas, one in the east and one in the south of the Netherlands. All MHCs selected a team of cognitive behavioural therapists that were willing to participate in our study. The number of therapists who treated patients with CFS varied between seven at the Eastern, two at the Western, and four at the Southern MHC. Each MHC also selected a team leader to coordinate the implementation of CBT for CFS.

All team leaders received the implementation manual of Scheeres et al. (13), which contained specific information about the use of CBT for CFS outside specialised treatment settings. This information included recommendations about selection, training and supervision of cognitive behavioural therapists, activities to inform potential referrers and patients about the new treatment option, and optimizing the patient flow from initial referral to the end of treatment, including routine assessment of fatigue and disabilities prior and subsequent to the treatment period. Treatment was based on the manual by Bleijenberg, Prins, and Bazelmans [14] and included goal setting, fixed sleep wake cycles, changing the focus on bodily symptoms, a systematic challenge of fatigue-related beliefs, regulation and gradual increase of activity, and the accomplishment of personalised goals.

The Eastern MHC sustained CBT for CFS from the study conducted by Scheeres et al. [12, 13]. Therapists at this MHC received supervision in CBT for CFS once a month for one and a half hour. The Western and the Southern MHCs had no specific experience with the treatment of CFS patients and both newly implemented CBT for CFS. Therapists received a CBT for CFS manual, a 4-day training, and supervision twice a month for one and a half hour. The training and supervision of therapists was provided by members of our research team. Implementation progress was discussed with the team leaders at biannual research meetings.

The Southern MHC also had a team of psychiatric nurses that delivered a low-intensity intervention for CFS in the context of a stepped care programme. The low-intensity intervention consists of written self-instructions on the basis of the manual by Bleijenberg et al. [14] and e-mail contact with a trained therapist [4]. There is evidence that stepped care for CFS is equally effective but more time efficient than face-to-face CBT alone [15]. Effects of the low-intensity intervention at the Southern MHC were examined in the context of an RCT that is outside the scope of this study [16]. In the present study, we focused on

data that were gathered during face-to-face CBT. Patients who were not improved following the low-intensity intervention were referred to face-to-face CBT as subsequent intervention. However, patients could also directly start with face-to-face CBT without following the low-intensity intervention (e.g., when they did not meet the inclusion criteria of the RCT).

Patients

Patients were referred by a general practitioner or consultant with the diagnosis CFS that implied that patients were suffering at least six months from severe and disabling fatigue in the absence of a medical explanation for the complaints as defined in the CDC criteria for CFS [1, 17]. These criteria were confirmed by a therapist of the MHCs upon intake. We included patients with a fatigue severity score of 35 or higher on the Checklist Individual Strength (CIS) and a score of 65 or less on the physical and/or social functioning scale of the Short Form Health Survey (SF-36) at baseline assessment. All patients were at least 18 years of age.

Measures

The subscale Fatigue Severity from the CIS was used to indicate the level of fatigue [18, 19]. This scale consists of eight items that are scored on a seven-point Likert scale. The sum score varies between 8, no fatigue, and 56, very severe fatigue. The cut-off score for severe fatigue was 35 (or higher). The level of disabilities was measured with the subscales Physical and Social Functioning from the 36-item SF-36 [20]. The scores on both scales range from 0, maximal limitations, to 100, maximal functioning. The cut-off score for severe disabilities was 65 (or less) on physical and/or social functioning. The level of fatigue and disabilities was assessed prior and subsequent to the treatment period.

Data collection

We monitored the implementation data in collaboration with the MHCs who provided routinely collected and anonymised patient information on a regular basis to us. This information included the number of patients per stage of the patient flow (i.e., referral, start of treatment end of treatment) and the assessment of fatigue and disabilities. Data were collected between June 2008 and February 2011.

Evaluation

Implementation process

Consensus was reached prior to the study that at least 40 patients should be included per MHC to be able to draw meaningful conclusions about the implementation of evidence-based practice for CFS. We defined dropout as not having completed second assessment. An

upper limit of 37% dropout from intention-to-treat to second assessment was considered to be tolerable. This proportion was derived from a study by Quarmby, Rimes, Deale, Wessely, & Chalder [21], who reported about dropout outside randomised trials in the context of CBT for CFS.

Treatment outcome

We determined the number of clinically improved patients with a reliable change index of >1.96 on the CIS fatigue severity, a fatigue severity score of <35 and a SF-36 physical functioning score of >65. We followed the statistical benchmark procedure of Scheeres et al. [12] using an uncontrolled pre−post benchmark effect size for fatigue severity and physical functioning which was calculated as (Mean $_{\text{baseline}}$ − Mean $_{\text{post-treatment}}$) / pooled *SD*. Effect sizes that were within the 95% confidence interval of the statistical benchmark were considered to be similar to the uncontrolled effect sizes of CBT for CFS in RCTs.

Effect sizes were computed on the basis of intention-to-treat but patients who were still in treatment at the end of our study were excluded from the analyses. Missing data from patients who decided not to start with treatment or who were no longer in treatment and had not completed second assessment were imputed as last observation carried forward.

Results

Implementation process

As described, we defined success in terms of the implementation process as 40 or more inclusions per MHC with a maximum dropout rate of 37% from intention-to-treat to second assessment. Each of the three MHCs fulfilled these criteria at the end of the implementation period (Table 1). Analysis of baseline characteristics revealed that dropouts had significantly higher levels of pre-treatment fatigue than completers ($p \leq 0.05$). Mean fatigue in dropouts was 53.2 (*SD* = 3.9). Patients who completed second assessment had a mean of 50.7 (*SD* = 5.2). Differences in age, gender as well as physical and social functioning were not significant. Halfway through the implementation process, our monitoring data revealed less inclusions than expected at the two new MHCs. Also, all MHCs had problems with the inclusion to completion ratio (Table 1). These problems were most obvious at the Southern MHC where 1 out of 16 included patients had completed second assessment after 15 months of implementation. We discussed these data at one of the biannual research meetings with all team leaders and agreed to provide external support in addition to the implementation manual to optimise the use of CBT for CFS.

This support was provided during the second half of the implementation period by members of our research team to the team leaders and administrative employees of the Western and Southern MHCs where CBT for CFS was newly implemented. It was delivered on the basis of an informal assessment of potential implementation barriers using the monitoring data and our communication with the team leaders of the MHCs. We did not intervene in the sustaining process of the Eastern MHC that did not express a need for additional support.

The additional support included monthly feedback about the monitoring data for the team leaders of the Western and the Southern MHCs to enhance awareness of the implementation progress. This feedback contained an overview of the patient flow such as the number of included and treated patients, the average time patients waited for treatment, the average treatment time and information about the use of assessments. This information was interpreted by us in terms of implementation success (i.e., how many more inclusions and completers are needed and what is the tolerable dropout rate). We provided

Table 1. Implementation process data per MHC

	Eastern MHC	Western MHC	Southern MHC
Inclusion	75	40	48
Mean age (*SD*)	37.2 (11.6)	32.3 (10.8)	42.6 (10.8)
Female	63 (84%)	30 (75%)	40 (83%)
Treatment			
Started*	67	39	47
Completed**	43 (64%)	33 (85%)	32 (68%)
Mean sessions (*SD*)***	11.5 (5.3)	12.8 (3.6)	10.3 (4.5)
Dropout			
Waiting for treatment	8/75 (11%)	1/40 (3%)	1/48 (2%)
During treatment*	15/58 (26%)	5/38 (13%)	5/37 (14%)
Intention-to-treat*	23/66 (35%)	6/39 (15%)	6/38 (16%)
1st half of the process**			
Included	43	21	16
Completed	8	5	1

Percentages may not equal 100 because of rounding. *Some patients were still in treatment at the end of the study. **Based on completion of second assessment. ***Based on completers. ****Based on data available at Sept. 2009.

administrative employees with information about missing data. In some cases, we assisted in the assessment of fatigue and disabilities. We also provided administrative employees with information about potentially stagnating treatments (i.e., treatment periods of more than six months). At the Western MHC, we supported the adoption of the monitoring system by one of the therapists due to structural problems at the level of the administrative employees.

We also stimulated both team leaders to intensify their patient recruitment activities and to optimise the patient flow for CFS patients at their MHCs in accordance with the implementation manual to increase the number of inclusions and to improve inclusion to completion ratios. At the Western MHC, we stimulated personal presence at meetings of general practitioners and publications in local newspapers. At the Southern MHC, activities were stimulated that focused on motivating patients to continue with treatment after ineffective low-intensity interventions for CFS. Only 10 of the 23 patients (43%) who were eligible to continue their treatment in the context of stepped care halfway through the implementation period had actually started with face-to-face CBT. We also stimulated team leaders to reduce prolonged waiting and treatment periods to avoid patient attrition.

At the end of our study, the team leaders of the Western and Southern MHCs reported that the external support helped them to gain more insight into the progress of their implementation and at the same time helped everyone to keep focused and motivated during the implementation process. All team leaders appreciated the fact that they were able to determine how much additional support was provided.

Treatment outcome

Treatment outcome data per MHC are presented in Table 2. Besides the number of clinically significant improved patients, we calculated uncontrolled effect sizes for fatigue severity and physical functioning. We defined success in terms of treatment outcome as uncontrolled effect sizes that were inside the range of the 95% confidence intervals of the statistical benchmark. The Eastern and Western MHCs both had effect sizes that ranged within these confidence intervals. The effect sizes for face-to-face CBT at the Southern MHC were significantly lower than the effect sizes of the statistical benchmark.

In total, forty-eight patients were included for face-to-face CBT at the Southern MHC. fifty percent of the patients (n = 24) had received a low-intensity intervention for CFS before face-to-face CBT in the context of stepped care. Two of these patients were still in treatment at the end of the study. Four patients (18%) showed clinically significant improvement. The

Table 2. Treatment outcome data per MHC

	Eastern MHC	Western MHC	Southern MHC
Intention-to-treat*	66	39	38
Clinically sign. Improved (%)	26 (39%)	26 (67%)	9 (24%)
Mean Δ fatigue (SD)	-13.9 (15.6)	-24.0 (18.7)	-8.6 (13.4)
Uncontrolled effect size	1.19	1.76	0.88
Statistical benchmark**	0.97-1.89	0.97-1.89	0.97-1.89
Mean Δ phys. functioning (SD)			
Uncontrolled effect size	14.8 (21.2)	29.9 (26.8)	10.3 (22.0)
Statistical benchmark**	0.65	1.23	0.43
	0.63-1.44	0.63-1.44	0.63-1.44
Completers***	43	33	32
Clinically sign. improved (%)	26 (60%)	26 (79%)	9 (28%)
Mean Δ fatigue (*SD*)	-21.3 (14.7)	-28.4 (16.9)	-10.2 (14.0)
Mean Δ phys. functioning (*SD*)	23.0 (22.3)	35.3 (25.6)	12.2 (23.5)

*Patients who were still in treatment were excluded. **95% confidence interval derived from Scheeres et al. 2008. ***Patients who did not complete second assessment were excluded.

other 50% (*n* = 24) of the inclusions had not received a low-intensity intervention for CFS prior to face-to-face CBT. Eight of these patients were still in treatment at the end of the study. Five patients (31%) showed clinically significant improvement.

Discussion

Implementation process

The purpose of the present study was to examine whether MHCs are able to implement and sustain CBT for CFS with the help of the implementation manual introduced by Scheeres et al. [13]. All three MHCs included at least 40 patients and none of the MHCs exceeded the tolerable dropout rate of 37% from intention-to-treat to second assessment. Contrary to original expectations, however, we provided additional support to the two new MHCs during the second half of the implementation process. This support included assistance for the team leaders in translating the implementation manual into practice and administrative employees in processing the monitoring data into meaningful feedback for those involved in the implementation process.

We believe that the additional support helped the new MHCs to increase their insight into the specific challenges of implementing CBT for CFS including potential ways about how to cope with these challenges. Yet, due to the design of our study, which lacked a proper control condition, we cannot say in what way our support ultimately influenced the implementation process of these MHCs. It is obvious, although, that we seem to have underestimated the need for supervision of those professionals who were not directly involved in the treatment of patients [22]. Consistently, our implementation manual does not seem to substitute external assistance for team leaders and associated professions. However, on the basis of our experiences with the initial implementation of CBT for CFS in the Eastern MHC [12], the implementation manual does seem to have the potential to make this assistance more efficient that would be of advantage for large-scale implementation of evidence-based practice for CFS.

Although the Eastern MHC had problems during the implementation process as well, this MHC was capable of sustaining CBT for CFS without additional support. It is possible that the relatively high dropout rates of this MHC would have been lower if we had provided additional support. Yet, as this problem was already addressed by Scheeres et al. [12] with limited success, these dropout rates may concern a structural problem of the MHC that might have been hard to influence by the professionals involved in the implementation of CBT for CFS. Critical to us in the decision not to deliver external support was the fact that the Eastern MHC did not express a need for additional assistance. The level of implementation support might thus best be adapted to the specific needs of individual MHCs in future implementations until more data are available.

Treatment outcome

According to the statistical benchmark, effect sizes of the Eastern and the Western MHCs were similar to the uncontrolled effect sizes of CBT for CFS in RCTs. This result is another promising finding for future implementations of CBT for CFS outside specialised treatment settings. At the same time, the Southern MHC had significantly lower effect sizes than the statistical benchmark. There are several explanations that may account for this finding. One possibility is that therapists at the Southern MHC may have been less effective in treating CFS patients according to the evidence-based standard. A study in the context of manualised CBT for CFS showed that therapists inside specialised settings do not affect treatment outcome [23]. However, on the basis of our monitoring data, we found that therapists in community-based settings seem to differ in their efficacy that might be due to their attitude towards working with treatment manuals [24].

Another possible explanation for the differences in effect sizes is the specific implementation scenario of the individual MHCs. In particular, the Southern MHC implemented more than one cognitive behavioural intervention at the same time in the context of a stepped care programme for CFS. None of the cognitive behavioural therapists were specifically trained for face-to-face contact with patients who already had received an ineffective low-intensity intervention which may have biassed treatment outcome in disadvantage of this MHC. In particular, uncomplicated patients who are likely to respond to treatment might have been filtered out at the level of the low-intensity intervention. A more complex subpopulation of CFS patients in face-to-face CBT at the Southern MHC might have been the result. Although the number of patients was too small to test these differences statistically, our clinically significant improvement rates indicate that face-to-face CBT for patients who had received the low-intensity intervention may have been less effective than face-to-face CBT for patients who had not received the low-intensity intervention.

We believe that an interaction of factors at the level of the therapist and the level of the treatment setting is most likely to explain our findings. Unfavourable attitudes of therapists towards manualised therapy before the implementation had begun may have been reinforced by a complex patient population for which there were no specific recommendations in the standardised treatment manual. This may have caused these therapists to try alternative strategies. Leaving the evidence-based procedure, in turn, may have inhibited established treatment effects.

On the basis of these findings, we would discourage implementation of the low-intensity intervention before therapists had sufficient time to develop a routine in face-to-face CBT. Extra therapist training may in addition help to warrant that therapists feel sufficiently prepared to meet the specific challenges of patients who did not respond to the low-intensity intervention. When these conditions are met, stepped care may be as effective in community mental health care, as it has been found to be in a specialised tertiary setting [15]. Refusals of face-to-face CBT after ineffective low-intensity interventions should be separately addressed in future studies, as this was a problem in the specialised setting as well.

Limitations

Apart from the naturalistic study design that lacked proper control conditions, there are other limitations to our study. Due to the heterogeneity of community-based mental health care, our findings may not fit seamlessly into other settings in and outside the Netherlands. Although we paid attention to factors that may be relevant for future implementations in our selection of MHCs (e.g., rural and urban regions are represented as well as different

implementation scenarios), future research will have to demonstrate how well our findings generalise to these settings.

The generalisability of our findings may also be limited by the fact that therapists knew that their treatments would be monitored in the context of a scientific study. Routine outcome monitoring is an element of evidence-based practice for CFS. Anonymised CBT for CFS data could thus be gained outside the context of scientific studies in the future, e.g., by using health care insurance data. These data could be compared with our findings to exclude the possibility of a bias due to observation.

As we do not have any follow-up data, we also do not know whether treatment effects are stable in patients who were treated in community mental health care. Future studies should test whether patients benefit persistently from evidence-based practice for CFS that was delivered outside specialised treatment settings. It would also be interesting to gather follow-up data on the treatment effects of the Southern MHC to find out whether effect sizes will increase and which factors may have contributed to such an increase.

Conclusions

Our findings suggest that MHCs are capable of implementing CBT for CFS with convenient effect sizes and tolerable dropout rates on the basis of intention-to-treat. At the same time, our data suggest that the implementation of stepped care for CFS is more complex than implementing face-to-face CBT alone and deserves additional attention and preparation. In particular, implementation of the low-intensity intervention may better be postponed until therapists have gathered sufficient experience with face-to-face CBT. Contrary to our expectations, our implementation manual does not seem to substitute external support but may help to make this support more efficient for large-scale implementation of evidence-based practice for CFS. The implementation manual could be improved on the basis of these and upcoming findings.

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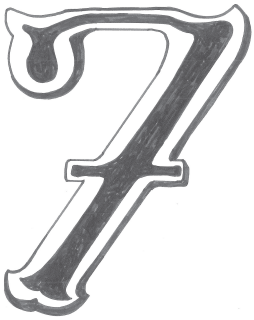
6

General discussion

In this final chapter, the results of the studies of this dissertation will be discussed. A distinction will be made between the practical implications of findings (Part I) and how findings relate to the existing literature on implementation of evidence based treatments for Chronic Fatigue Syndrome (CFS) (Part II). As previously mentioned, in the Netherlands there is limited availability of cognitive behavioural therapy (CBT) for CFS. If this availability increases, more CFS patients can be treated with CBT, which would not only decrease patient suffering, but also decrease the costs of CFS to society, which are related, among others, to medical expenses, work absenteeism, and costly career changes. The Expert Centre for Chronic Fatigue has over the past years conducted studies on possibilities for implementation of treatment for CFS outside specialised treatment centres. The results of this research are described in Chapters 4 and 6 of this dissertation. A logical next step is to expand the implementation of treatment for CFS to other mental health centres with the aim to work toward national implementation of stepped care for CFS. In 2011, we described the steps toward this goal in an article that was published in the journal Gedragstherapie. This article is reprinted here as Part I of the discussion.



General discussion

Part I:
The necessity of national implementation of stepped care for chronic fatigue syndrome

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Summary

Approximately 30 000 to 40 000 patients in the Netherlands suffer from chronic fatigue syndrome (CFS). Currently, treatment options for these patients are limited: the need for treatment is higher than can be delivered. In recent years, research has been done into the possibility of implementing cognitive behaviour therapy (CBT)—one of the few treatment approaches to CFS that has proven to be effective—into MHCs. This appears to be a possibility, providing that CFS specialists are involved in this process. Recently it has been shown that a minimal intervention—guided self-instruction with email support—based on CBT for CFS is effective in the reduction of disabilities and fatigue. These two approaches, guided self-instruction and individual CBT, constitute a stepped care approach for CFS. It is desirable to implement this model nationally, so that all CFS patients can receive effective treatment—regardless of their geographical location. In this article, concrete steps that are necessary for successful national implementation for treatment of CFS are described.

Introduction

When is someone affected by CFS?

Most people experience fatigue on a daily basis. The next morning, or after rest, this fatigue has disappeared. If fatigue is severe, lasts longer than six months, and is accompanied by limitations in functioning, then this could be indicative of chronic fatigue syndrome (CFS)—even more so if there are additional symptoms such as muscle aches, joint pain, headaches, and problems with concentration or memory. We only speak of CFS when there is no medical explanation for the fatigue. In the Netherlands, approximately 30 000 to 40 000 patients suffer from CFS [1, 2], though a recent study suggests that these numbers may be far higher [3].

What are treatment options?

Cognitive behaviour therapy (CBT) is one of the few treatment approaches to CFS that has shown to be effective [4, 5]. CBT for CFS aims at changing cognitions and behaviours that sustain the fatigue. Important elements in this type of treatment are changing the dysfunctional fatigue related cognitions (increasing self-efficacy and reducing catastrophising and excessive focus on bodily symptoms), and an increase in activity levels [2]. CBT is effective, but appears to be a difficult treatment approach for health-care professionals and patients alike [6]. It is intensive, requiring 13 to 16 sessions with highly specialised cognitive behavioural therapists. In the past years, CBT for CFS has been implemented in three Mental Health Centres (MHCs), but national treatment capacity for CFS in the Netherlands is still insufficient. Expansion of treatment possibilities is crucial to ensure that more patients with CFS can receive the care they need.

What is stepped care for CFS?

Stepped care ensures that a patient gets the kind of care he or she needs. Step one in a stepped care model for CFS is guided self-instruction supported by email. Guided self-instruction is comprised of a workbook with instructions that are based on the CBT protocol for CFS. This treatment is carried out independently in the patient's home, supported by email communications with a cognitive behavioural therapist. This minimal intervention is followed by individual CBT for CFS if step one was insufficiently effective or if even prior to guided self-instruction it was clear that the minimal intervention will not suffice. A randomised controlled study in a third line health care facility centre showed that guided self-instruction with support via email is effective [7]. The model of stepped care was also tested for efficacy in a CFS centre and found to be effective (Chapter 3) [8].

Where can stepped care for CFS be implemented?

Institutions or organisations have to meet a number of criteria in order to be eligible for implementation of a stepped care program for CFS. Multiple psychologists have to be employed at the facility to enable peer review and consultation and to ensure that the skills learned are maintained. It is also crucial that the psychologists are licensed cognitive behavioural therapists (in training) with time for and interest in training and supervision. In addition, the organisation or facility has to be able to offer 13-16 treatment sessions. Two organisations meet these criteria for implementation of CBT for CFS: first line practices and MHCs. Hospitals were not eligible because general practitioners in the Netherlands cannot directly refer a patient to a psychologist in a hospital. These patients are often first referred to a medical specialist (neurologist or internist) who often orders additional medical procedures, leading to unnecessary additional costs.

Psychologists in the first line have experience working with patients with physical symptoms, which makes this setting potentially suitable for implementation of stepped care. However, CBT for CFS is a long-term treatment for which first line practices are unlikely to be fully reimbursed by insurers. First line practices are also often based on sole proprietorship, which makes peer review and consultation impossible.

MHCs are more suitable for implementation of stepped care for CFS. The specialised nature of CBT for CFS fits well with current developments in these institutions and MHCs are familiar with CBT as an approach to psychotherapy. Issues such as anxiety and depression are already successfully being treated with CBT in MHCs, and there are numerous trained therapists there who can be trained to treat CFS with CBT. This also ensures continuity in care—should one health-care professional become unavailable—the knowledge gained regarding treatment of CFS is not lost. For these reasons, it is our preference to implement stepped treatment for CFS in MHCs.

Method of implementation

Which steps are needed for implementation?

In 2003, implementation of CBT commenced at GGnet, an MHC in the eastern part of the Dutch province of Gelderland. After three years, the process as well as impact of the treatment was examined. It appeared that it was possible to implement CBT for CFS under certain conditions [9]. These conditions are outlined in manual, which can be used by other MHCs that have an interest in the implementation of CBT for CFS [10]. The most important conditions are listed below. Organisation/management/therapists have to be willing to:

1. Make therapists trained in behavioural therapy available for training and supervision so that there is sufficient expertise to ensure that execution of treatment is in keeping with quality standards.

Experience has taught us that CBT for CFS is a difficult treatment, which is only effective when done by cognitive behavioural therapists who are trained in CBT for CFS [11]. In order to be eligible for training for CBT for CFS, therapists have to have completed a basic course in behavioural therapy that is recognised by the Dutch association for behavioural and cognitive therapies (VGCt). These therapists also have to be cognitive behavioural therapists in training with VGCt. A certification regulation is in place to ensure that (1) CFS patients are treated by experienced and well-educated therapists, who (2) evaluate their treatment thoroughly, who (3) use specific instruments for this evaluation, and who (4) undergo additional training and professional development (for more information, see www.umcn.nl/cv). The difficulties in treatment for CFS include motivating patients, preventing dropout, identifying and challenging relevant cognitive patterns, establishing recovery as treatment goal, solving problems when regulating activities, dealing with complaints and symptoms of pain, establishing and implementing back-to-work plans, and dealing with co-morbidity [2, 11].

Patients with CFS are new to MHCs, and it is important that therapists learn to understand and work with patients who attribute symptoms to somatic causes. Motivating patients at the start of therapy is an art and crucial at the same time, as creating the right conditions increases the chance of positive treatment outcomes. The (change in) attitude in the patient is an important element in this. Supervision for one to two years, depending on intensity of treatment and case load by a cognitive behavioural therapist who has specialised in CFS is necessary to ensure that the treatment is done right, plus it is also a condition for certification. In the training of CBT for CFS, thorough attention is given to the treatment protocol to enable therapists to work with it. Nonetheless, therapists will -especially in the first few years- encounter challenges. These need to be openly discussed so that the therapist can carry on in confidence and make the right decisions.

2. Create organisational conditions to better enable patients with CFS to enter treatment.

Organisations need to implement an intake program specifically for patients with CFS. These patients should not enter a general intake procedure but be immediately referred to a CBT therapist for CFS. CFS patients often attribute their symptoms to physical ailments, which does not match a typical intake at an MHC. A regular intake does not suit the experience of the symptoms, which can lead to premature dropout. A specific intake with direct attention to CFS is needed. Better intake of patients with CFS can be achieved through something as simple as an email address that referring health care professionals can use to refer patients with CFS.

3. Inform general practitioners, other health care professionals, and patients of treatment options.

Health care professionals are important for successful implementation of treatment for CFS. They need to be informed of the possibility to refer patients with CFS to an MHC. A variety of ways to convey information can help inform health care professionals about this new option. Health care professionals need not only to know about referral options, they also need to be able to recognise and diagnose CFS and motivate patients to enter treatment, so aside from knowing about treatment, physicians need additional educational materials regarding CFS. This can be thorny as physicians are bombarded with information. Therefore, it is helpful to repeat the information and to use a variety of channels to convey it. Repeated distribution of written information to physicians has proven to be effective, with 'repeated' meaning that at least four times in the first two years an informative letter and brochure is sent to health care professionals [12]. Aside from written materials, small-scale information sessions have also shown to be effective [12]. These sessions offer physicians an excellent opportunity to ask questions, engage in discussions, or express reservations, for example about a CFS diagnosis or treatment outcomes. A good way to organise such meetings is trough collaboration with district based physicians collectives. Having accreditation applications for physicians who attend the meeting will increase turnout.

4. Inform and familiarise other health care workers, so that patients with CFS enter the right treatment program.

As is the case with any specialised treatment, only a few select people are directly involved in the treatment for CFS. It is however also important that those less involved know the what, why, and how of the new treatment to prevent patients with CFS from entering into

the wrong treatment trajectory. To prevent wrong referrals, especially those working in intake and screening and those who manage programs need to be well informed. MHCs have many employees who work in different locations, so informing everyone is no simple task. Ways to inform as many people as possible include on-site presentations at one or more locations, and/or including an article about the new treatment and referral options in a newsletter for employees.

5. Measure patient symptoms and limitations before and after treatment so that treatment outcomes can be made transparent and used for follow-up of referring health care professionals.

Treatment of CFS is aimed at recovery-not at learning how to cope with fatigue. In order to know whether this goal has been achieved, treatment needs to be evaluated with reliable and valid instruments such as the Checklist Individual Strength (for fatigue) [13] and the Medical Outcomes Survey Short Form-36 (for impairment) [14, 15]. Dutch norms for the scales are available. Evaluation of treatment outcome is also a condition for certification. Without evaluation it is impossible to know whether the health care facility is capable of effectively treating CFS. More importantly, therapists and patients need to be clear on whether (sufficient) improvement has ensued from the intervention. It is useful to share this information in the final session with the patient.

Results

What are the experiences with implementation of CBT for CFS in an MHC with use of the manual?

Based on the experiences with the 2003 project, a practice project aimed at implementation of CBT for CFS commenced in collaboration with three MHCs: 'GGnet', 'GGZ Westelijk Noord-Brabant', and 'PsyQ Rijnmond'. Over the course of two and a half year, data about the treatment of CBT was collected. Health care professionals at 'GGnet' wanted to continue to use the already implemented treatment. 'GGZ Westelijk Noord-Brabant' and 'PsyQ Rijnmond' implemented CBT for CFS with use of the manual. Each facility was awarded a budget to appoint an officer to organise the implementation internally and to ensure continuity of care. The role of the specialists in the treatment of CFS was limited to the training and supervision of therapists.

'GGnet' was able to carry on their treatment programs at a similar level. The issue of relatively high dropout rates of patients during intake and treatment—something that has been observed in the earlier implementation—was not solved. This dropout is partly preventable

if patients can start immediately with intake and treatment. 'GGZ Westelijk Noord-Brabant' and 'PsQ Rijnmond' both had problems during the first year of the implementation, including getting referrals to come in for the new treatment options and problems in final stages of treatment. Therefore, half way through the project, more support was offered for the continuation of the implementation. Initiatives were made to recruit patients and the participating institutions were regularly offered feedback on the process. With this extra support, all facilities successfully implemented CBT for CFS. A full description of the results can be found in Chapter 6 of this dissertation [16].

The most important lesson learned from this project (i.e., implementation of CBT for CFS in collaboration with 'GGnet', 'GGZ Westelijk Noord-Brabant', and 'PsyQ Rijnmond') is that MHCs can offer high-end CBT for CFS, providing that there is sufficient external guidance from specialists in the treatment of CFS during the first two years. This external guidance is crucial to successful implementation additional to preparedness of the institutions to invest in the appointment of an officer to support the organisation of the implementation internally. During implementation and beyond, treatment outcomes need to be monitored in order to ensure quality of care as well as successful implementation.

Simultaneously with the aforementioned project, the first step in stepped care for CFS—guided self-instruction with support from a therapist via email—was tested in an MHC ('GGZ Westelijk Noord-Brabant') (Chapter 4) [17]. In a controlled, randomised trial it was examined whether psychiatric nurses, some with limited experience with behavioural therapy, can successfully execute the minimal intervention. The results of this trial show that after guided self-instruction, patients experienced significantly fewer symptoms related to fatigue. These results are as positive as those found in an earlier study in which the minimal intervention was guided by behavioural therapists [7].

Conclusion

Problems with implementation

Experience has taught us that during implementation, some problems may arise. We will describe these here in brief.

Recruiting patients. The number of patients that is referred to a new institution varies and depends on communication aimed to disseminate information. It is important that therapists treat at least six patients annually in order to gain enough experience for this specific work. It is therefore essential that during the initial phases, ample time and attention is dedicated to circulating information about the new treatment options.

Ending therapy. On average, new therapists treat patients longer than is prescribed in the protocol. The long treatment duration is often related to the experience level of the therapist, who may also be of the opinion that (further) recovery is still possible after the recommended treatment duration. However, long-term treatment (i.e., more than 20 sessions) is rarely helpful [2].

Evaluating treatment and follow-up. Pre- and post-treatment evaluation is not standard in all MHCs, but is important in order to gain insight into the success of the implementation. Especially a post-treatment evaluation reveals efficacy as well as weaknesses. In addition, health care professionals need follow-up regarding the patients they referred: What happened to those patients and how did treatment work out? Follow-up will make it more likely for referring health care workers to refer new candidates for treatment.

Monitoring and active support. Previous experience taught us that external guidance during implementation of a stepped care approach for CFS is crucial during the first two years. During this period, extra support needs to be offered, for example in the area of evaluation or motivating health care professionals to refer patients. After the first two years, institutions are able to carry on the treatment independently and in keeping with quality standards.

Why is national implementation needed?

In the Netherlands, there are many patients with CFS who, due to a lack of treatment capacity, cannot receive evidence-based treatment in the area where they live. Implementation of a stepped care for CFS in an MHC is possible and appears effective, providing there is additional support in the start-up phase. National implementation of stepped care for CFS seems a logical next step.

The relatively high costs for implementation, training, supervision, coordination, information dissemination, and maintenance is a barrier to this next step however, and initially, there will be a negative balance between investment and return. Depending on insurance reimbursements and number of patients, the stepped care program for CFS should be profitable within four to six years. Financial support would increase the willingness of MHCs to implement these treatments. In addition, CBT for CFS is a cost efficient treatment from societal perspective [9, 18]. Annual profits resulting from CBT for CFS are related to the decrease in medical consumption (fewer medical tests) and decrease in absenteeism (an increase in participation in the work force) are higher than the costs needed to implement and execute CBT for CFS. If health care professionals can diagnose CFS and refer patients directly to an MHC, then a visit to an internist or neurologist is rarely needed.

In closing, we argue in favour of implementation of stepped care for CFS. Patients with CFS need more treatment options so that they can receive treatment right away, and in their own geographical location. The treatments, guided self-instruction, and CBT have proved their efficacy. In the national implementation trajectory, therapists will be selected, trained, and supervised, to enable them to execute the treatments in the best possible ways.

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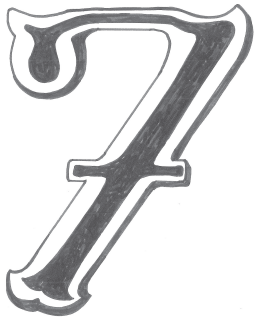

General discussion

Part II:
Chronic fatigue syndrome: a patient's journey

In the second part of the discussion, the results of the studies reported in this thesis will be discussed in the light of the literature on diagnosing and treating chronic fatigue syndrome (CFS). Possible implications of our findings for the treatment of CFS patients and suggestions for future research will be discussed. For this we will follow the patient's journey from diagnosis to treatment.

Diagnosing CFS in primary care

Fatigue is a common complaint in general practice [1]. Most of the patients with fatigue (75%) need only one consultation with their general practitioner (GP), and in 90% of the cases the fatigue lasts less than six months [2]. Occasionally, fatigue can become severe and interfere with normal life. When a patient presents with persisting and disabling fatigue for more than six months, GPs should consider the diagnosis of CFS [3, 4]. CFS is a clinical diagnosis made after excluding medical or psychiatric diseases that can explain fatigue. Correctly diagnosing CFS is necessary for appropriate referral for treatment. Not diagnosing CFS means withholding the patient from the possibility to reduce symptoms and even recover.

The NICE guidelines recommend that a diagnosis of CFS should be made in primary care [5, 6]. In the study described in chapter 2, we found a large discrepancy between the number of patients that might be considered as having CFS in primary care and the number of patients who were actually diagnosed as CFS. Others also showed that CFS is more common in primary care than recognised by the GP [7-9]. In a cross-sectional random sample of the adult female population in Nijmegen [9], more than 70% of the CFS-like group consulted their GP because of fatigue. Only 6 out of the 89 CFS-like subjects (6.7%), were actually diagnosed as having CFS. This indicates that CFS is under diagnosed.

Why does under diagnosis occur? Several reasons can be mentioned. GPs have limited knowledge about CFS [10, 11]. In a study performed in the Netherlands, more than 25% of the GPs reported they did not know how to diagnose CFS. In their opinion a medical specialist should diagnose CFS. GPs themselves often felt they were unable to adequately inform a CFS patient about the illness and the treatment options [11]. In the UK—before the NICE guidelines for CFS appeared—nearly half of the GPs reported lack of confidence in making a diagnosis of CFS [10]. Also more recent studies showed that GPs feel uncomfortable making a diagnosis of CFS [12, 13].

It is also known that some GPs have negative attitudes and scepticism towards CFS [14, 15]. Bowen et al. reported that in a UK primary care study 28% of the GPs did not accept CFS as a

clinical entity [10]. Negative attitudes towards CFS exist because the lack of a precise bodily location, reclassification of CFS over time, and doctor-patients miscommunications about causes and management [14]. In a qualitative study some GPs expressed the concern that a label of CFS can cause harm to the patient. The GPs felt there was no clear management pathway for either the GP or the patient [12]. These perceptions may be a barrier to effective illness management.

GPs as the gatekeepers of healthcare, apply a generalistic approach. If a person presents with fatigue, generalists exclude the presence of (chronic) diseases. They suggest that their role—in making a diagnosis of CFS—is to exclude physical causes for the patient's symptoms [12]. At the same time they try to understand the complaint in the context of the patient: the context–oriented approach. In the absence of a somatic disease, generalists try to explain fatigue as a consequence of what is happening in the patient's life. Therefore, generalists often assume that fatigue is a sign of psychosocial problems. Moreover, generalists are often reluctant to pay attention to somatic symptoms assumed to be part of psychosocial problems. This is similar to what we found in chapter 2. GPs saw fatigue as a symptom of psychosocial and psychiatric problems and therefore did not diagnose CFS. They considered the psychosocial problem as the central issue and expected that attention for somatic aspects of complaints would impede the solution of these problems. However, the presence of psychological problems is not an exclusion criterion for CFS, as long as fatigue is the main complaint [4, 16]. By focusing on the psychosocial problems, the generalist might withhold the patient from an effective intervention, i.e. CBT aimed at the cognitions and behaviour that perpetuate the fatigue.

Another possible explanation of under diagnosis of CFS might be found in the interaction between the GP and the patient. We found inconsistency between what patients reported to have mentioned during the consultation and what was registered in the electronic medical file (chapter 2). Potential barriers include the complexity of patients' problems and patients' judgements about how to manage their presentation of CFS [17]. As a result there may be some dissimilarity between the patients' complaints and what is presented. It is unknown what exactly happened during the consultations in the investigated general practice, as we did not record them.

How to improve diagnosis of CFS and prevent under diagnosis? It is necessary to convince GPs of the usefulness to diagnose CFS. GPs have to feel confident making the diagnosis, followed by a referral to an appropriate treatment. Our research group showed that GPs informed about CFS reported more positive attitudes towards CFS than non-informed GPs. Also, this study showed that GPs who did visit an information meeting about CFS referred

significantly more patients for treatment compared to GPs who did not visit the meeting [11]. This indicates that GPs referral behaviour can be influenced by written and oral information. Another way to reduce under diagnosis is that GPs use an instrument to detect CFS. This instrument should be simple and easy to use in clinical practice. A possibility is a short questionnaire—with dichotomous answers—that will help GPs to classify a person presenting with fatigue as CFS or non-CFS. This instrument should be tested in case studies, as it seems that GPs are more easily to convince by this kind of studies than by randomised controlled trials (RCTs) [18]. Additional, developing interactive training sessions on how to diagnose CFS—introduced in the medical curriculum of GPs—may help GPs to feel more confident to diagnose CFS. These training sessions can be based on the guidelines for CFS. Recently, the Dutch Institute for Healthcare Improvement (CBO) has developed a multidisciplinary guidelines on CFS (www.diliguide.nl/document/3435). The CBO guidelines suggest that the GP should consider a diagnosis of CFS if the patient fulfils the criteria for CFS without necessarily consulting a medical specialist for additional tests. Guidelines can help GPs to optimise the diagnosis and management of CFS and can make GPs more aware of treatment options and their effectiveness.

Minimal CBT interventions

Benett–Levy et al. (2010) developed a definition of minimal CBT interventions: "The primary purpose of minimal intensity CBT is to increase access to evidence-based psychological therapies in order to enhance mental health and wellbeing on a community-wide basis, using the minimum level of intervention necessary to create the maximum gain [19]." Three types of support in minimal intensity interventions can be distinguished: self-administered, minimal contact and guided self-help [20, 21]. In self-administered interventions support in the use of self-help is provided at any time with contact restricted to the research team regarding non-process issues. Patients who follow a minimal contact intervention are provided with a rationale for the use of the materials, which also may include regular contact regarding process but without any focus on process issues. During guided self-help interventions patients receive an initial support session in which the rationale is explained. During this session the patients receives material they can work through independently, while a therapist has contact with the patient at regular times to discuss progress and process issues [20, 21].

Efficacy of minimal CBT interventions for CFS

It is shown that minimal interventions can affect symptom report in (chronic) diseases [22-26]. This is also demonstrated for CFS [27-30] (Chapter 4) [31]. The table below gives an overview of the effects found in RCTs of minimal interventions for CFS (Table 1.) A study of

Chalder et al. was not included as this study investigated the effect of a self-help treatment for patients with chronic fatigue (not CFS) [32].

In summary, all studies showed that minimal interventions for CFS are effective in reducing fatigue. Some remarks can be made when comparing the studies. In three studies the intervention was carried out by cognitive behaviour therapists, whereas the other two studies selected nurses to guide the intervention. Wearden et al. [29] used the intervention described and carried out by Powell et al. [27] in a primary care setting, and found that pragmatic rehabilitation—as this intervention was called—was less effective compared to the previous trial. Therapist variations could be a possible explanation for this finding. In the first trial [27] the therapy was delivered by one very experienced therapist, who had developed the treatment. In the trial of Wearden et al. general nurses who had no previous experience with pragmatic rehabilitation or counselling for CFS were trained to carry out the therapy [29]. Although these nurses showed to be competent, the effect sizes were smaller. In our trial, chapter 4 [31], we showed that psychiatric nurses—novice with respect to CBT and the treatment of CFS but experienced in counselling—can be trained to deliver the minimal intervention effectively. Effect sizes for fatigue were similar compared to the trial where patients received support from experienced cognitive behaviour therapists [28, 31]. Also some other possible explanations for the dissimilarity between the studies of Wearden et al. and Powell. et al. and our studies can be mentioned [27-31]. First, Wearden et al. included more severely affected patients compared to the trial of Powell et al. [27, 29]. We did not find differences in the characteristics of the patients between our two trials [28, 31]. Second, delivering the treatment in patients' homes causes different barriers compared to delivering the therapy in a healthcare setting [27, 29]. Our interventions, guided self-instruction, were carried out by patients at home, but guided by email contacts between patient and therapist [28, 31].

Only three of the five studies reported follow-up effects [27, 29, 30]. The studies performed in our centre [28, 31] could not assess follow-up effects. In both studies patients were offered regular CBT if the minimal intervention did not lead to the desired effect. As a consequence measuring follow-up effects will lead to bias, as only follow-up effects after successful guided self-instruction can be collected. The other studies showed contradictory follow-up effects. Improvement of fatigue and physical functioning after telephone CBT was maintained at one year follow-up [30]. Also Powell et al. reported that positive effects were maintained at one year follow-up [27]. This in contrast with the study of Wearden et al. who did not find that post-treatment results maintained at follow-up [29]. In order to be an alternative to regular CBT, treatment effects should be sustained over time as is the case with regular CBT [33, 34].

There seem to be differences in effect between minimal interventions providing support by mail and minimal interventions providing support by telephone. Burgess et al. compared face-to-face CBT with telephone CBT for CFS [30]. They showed that telephone CBT is non inferior to face-to-face CBT (Table 1). This is not what we found when comparing the minimal intervention with regular CBT (Chapter 3) [35]. The percentage of patients with clinically significant improvement after guided self-instruction, 27% [28], was considerably less than after regular CBT, 48% (Chapter 3) [35], indicating that regular CBT is more effective in reducing fatigue than guided self-instruction. It would be useful to compare effect sizes of both interventions, but this is impossible because the lack of a control group receiving no treatment in the study of Burgess et al. [30]. Percentages of clinical improvement are mentioned, but different criteria are used and therefore not comparable. Additionally, it has to be mentioned that total therapist time during telephone CBT (526 minutes) is substantial higher compared to guided self-instruction (316 minutes). The same goes for the percentage of dropout, respectively 36% and 7%. The considerably percentage of dropouts may question the findings of Burgess et al. as this study performed a complete case analysis instead of an intention-to-treat analysis as we did in our study.

Telephone and email support differ in their advantages and opportunities for patients. During a telephone call, the patient receives immediate feedback in response to his input. Additional questions can be asked when the received feedback is not clear or not sufficient. On the other hand, communication by email is slower and consequently easier to follow. The patient has the opportunity to reread the feedback. In addition, email is available at any time. As a result telephone and email support may serve different needs and preferences. It is quite conceivable that patients with CFS prefer (and need) immediate feedback to change their behaviour. Through the development of communication tools, as for example Skype and Face Talk, immediate feedback during internet treatment of CFS seems implementable in the near future.

Finally, it is unclear how much support is necessary for a reduction of fatigue. There is a considerable variation in total therapist time (range: 246 – 683 minutes) between the studies presented in Table 1. Insufficient data were presented to compare the influence of level of support. Powell et al. and Burgess et al. did study the effect of different levels of support within their study. In both studies, no differences in effect were found for the diverse levels of support [27, 30]. None of the minimal interventions for CFS examined if a self-administered intervention (without support of a therapist) can lead to a significant reduction of fatigue and disabilities. For depression, several studies tested whether a minimal intervention without therapist support is effective. Some studies found positive effects of support [25, 36], whereas others didn't [37, 38]. For minimal interventions for CFS the impact of support is unknown. Future studies should focus on this issue.

Predictors and moderators of treatment outcome

Several studies investigated predictive and moderating factors of treatment outcome in patients with CFS [34, 39-47]. A predictor or moderator is a variable that can predict outcome, for example reduction of fatigue. Only one study investigated predictors of treatment outcome in minimal interventions for CFS [28]. It was showed that a subgroup of patients with high levels of fatigue and disabilities profited less from the minimal intervention [28], suggesting that patients with very severe symptoms could perhaps better directly be referred to regular CBT. In chapter 5 we showed that patients with stronger avoidance of activities and patients with more severe depressive symptoms do not benefit as much from the minimal intervention as those who have low tendency to avoid activity and those who do not have severe depressive symptoms. Patients with clinically relevant depressive symptoms may have better treatment outcomes if they are directly referred to CBT, as depressive symptoms do not seem to predict outcome in regular CBT [45]. Additionally patients' expectations at the start of CBT for CFS seem predictive of treatment outcome [48]. Patients with very positive outcome expectations had a larger reduction in fatigue than patients with less positive expectations. It is likely this also applies to the minimal intervention. Therapists need to pay attention to the patients' beliefs and expectations of the minimal intervention they offer. Future research should focus to assess patients' suitability for the minimal intervention. By identifying predictors and moderators of treatment outcomes it can be determined which patients can best be directly referred to CBT and which patients should be offered a minimal intervention. In this way treatment efficacy and efficiency can be enhanced.

Mechanisms of change

Although minimal interventions for CFS are effective in reducing fatigue and disabilities, little is known about the specific mechanisms of change. Mediation analyses are a way to obtain insight in the process in which a variable intervenes in the relationship between treatment and outcome [49, 50]. Wiborg et al. [51] used a structural equation model to test whether changes in focusing on symptoms, perceived problems with activity, and sense of control over fatigue mediated the effect in a minimal intervention of CFS [28] for fatigue and disabilities. Mediation analysis showed that a decrease in perceived problems with activity and an increase in sense of control of fatigue contributed to the treatment effect of the minimal intervention for CFS [51]. In other words change of perception and beliefs of activity and fatigue in minimal interventions for CFS is necessary for effectiveness. Future research must replicate these findings in order to validate the treatment model. Also changes in other factors as for example self-efficacy with respect to activity, catastrophising and sleep-wake disruption have to be investigated to test whether they also mediate the effect in a minimal intervention.

Table 1. Overview of minimal interventions for CFS

Randomisation	Description of the content of the intervention	Level of support
Powell et al. (2001) [27]		
Standardised medical care (SDM) (*n* = 34) Minimum intervention (MIN) (*n* = 37) Telephone intervention (TEL) (*n* = 39) Maximum intervention (MAX)(*n* = 38)	The interventions groups all received an educational pack describing the role of disrupted physiological regulation in fatigue symptoms and encouraging home based graded exercise.	Minimal contact
Knoop et al. (2008) [28]		
Guided self-instruction (GSI) (*n* = 85) Waiting list condition (WLC) (*n* = 86)	GSI consisted of a self-help booklet containing information about CFS and assignments combined with email contact.	Guided self-help
Wearden et al. (2010) [29]		
Pragmatic rehabilitation (PR) (*n* = 95) Supportive listening (SL) (*n* = 101) GP treatment as usual (GP) (*n* = 100)	PR: similar to the interventions of Powell et al. (2001). Level of support was different. SL: provided emotional support.	Minimal contact
Burgess et al. (2012) [30]		
Face to face CBT (FCBT) (*n* = 35) Telephone CBT (TCBT) (*n* = 45)	FCBT: regular CBT for CFS. TCBT: patients received a folder containing a treatment manual, activity, sleep and thought diaries to complete.	Guided self-help
Tummers et al. (2012) Chapter 4 [31]		
Guided self-instruction (GSI) (*n* = 62) Waiting list condition (WLC) (*n* = 61)	GSI: similar to the intervention of Knoop et al. (2008).	Guided self-help

Table 1. Overview of minimal interventions for CFS (continued)

Mean total therapist time (min)	Therapist	Effect of the intervention on fatigue and physical functioning	Percentage of drop-out (%)	Follow-up effects
Powell et al. (2001) [27]				
MIN: 246 TEL: 452 MAX: 683 Duration: 3 months	1 CBT therapist	Significant reduction of fatigue and increase of physical functioning. No differences between intervention groups.	SDM: 5 MIN: 14 TEL: 18 MAX: 18	Maintained at 1 year follow-up
Knoop et al. (2008) [28]				
GSI: 316 WCL: 120 Duration: ≥16 weeks	6 CBT therapists trained in CBT for CFS	Significant decrease in fatigue and physical disabilities.	GSI: 7 WLC: 5	unknown
Wearden et al. (2010) [29]				
PR: 600 SL: 600 Duration: 20 weeks	3 general nurses, received training and supervision	PR: significant reduction in fatigue not in physical functioning SL: poorer physical functioning and no difference in fatigue	PR: 11 SL: 4 GP: 8	Not maintained at 70 weeks follow-up
Burgess et al. (2012) [30]				
FCBT: 787 TCBT: 526 Duration: unknown	8 trained CBT therapists who had worked at the department for at least 6 months	Significant reductions in fatigue and physical functioning. No significant differences between the interventions.	FCBT: 17 TCBT: 36	Maintained at 1 year follow-up
Tummers et al. (2012) Chapter 4 [31]				
GSI: 276 WLC: 30 Duration: ≥16 weeks	8 trained psychiatric nurses, received training and supervision	Significant decrease in fatigue. No significant difference in physical functioning.	GSI: 11 WLC: 8	unknown

Further development of a model of stepped care for CFS

In a model of stepped care, different levels of care can be offered to the patient, with the aim of delivering the least care necessary to treat a patient adequately. At this moment the model of stepped care for CFS distinguishes three levels. As a first step, guided self-instruction can be offered to the patient. Additional the patient can receive CBT delivered at a mental health centre (MHC). Next, as a third step, patients who do not recover can be referred to specialised treatment settings, as the Expert Centre for Chronic Fatigue. Only the first two steps are tested and evaluated. Later, other steps can be added. For example, personalised medicine can be introduced based on patients' preferences or characteristics that make a patient likely to profit from an intervention. The first step could be offering a self-instruction booklet, for instance by internet, without support of a therapist. If this treatment does not have the desired effect or if patients do not want this type of minimal intervention without professional help, the next step can be offered: self-instruction with support (guided self-instruction). Further development of a model of stepped care means formulating criteria to determine when a patient goes on to the next step. For example, for some patients it will be immediately clear that the first step, guided self-instruction for CFS without face-to-face contact with a therapist, will be insufficient. In that case patients need to be directly referred to the second step, regular CBT for CFS. At this moment the indications for assignment to a specific step are: (1) the patient does not want guided self-instruction; (2) the impairment in daily life is extreme; and (3) presence of severe depressive symptoms. For the moderator avoidance of activity it is difficult to establish a strict cut-off point for assignment to a specific step.

Barriers and facilitators of implementation

Despite comprehensive research to barriers and facilitators of implementation, there is a gap between controlled scientific trials and daily clinical practice [52-54]. Many treatments have been tested in RCTs, but only a few have been examined in clinical practice. The barriers and facilitators of implementation for treatment for CFS have been discussed in Part I.

Only three studies evaluated the efficacy of implementation of CBT for CFS in clinical practice settings [55-57] (chapter 6). Quarmby et al. compared the treatment results of an RCT to clinical routine outcomes of a specialised treatment centre. Between baseline and follow-up measurement (six months), the RCT showed greater effect sizes than treatment in routine practice [55]. Scheeres et al. (2008) performed an implementation of CBT for CFS in an MHC. Intention-to-treat effects were compared to the outcome of four RCTs of CBT for CFS. Outcomes of the implementation study did meet the benchmark. In other words, the results showed that CBT for CFS can be effectively implemented in an MHC [56]. The latest implementation study is described in chapter 6 [57].

Implementation of stepped care for CFS

The study described in chapter 3, is the first study so far that evaluated a model of stepped care for CFS. It showed that stepped care for CFS is as effective as regular CBT, while it is more time efficient for the therapist (chapter 3) [35]. In chapter 6 it is illustrated that one of the MHC's implemented CBT in the context of stepped care for CFS. This MHC showed significantly lower effect sizes than the effect sizes of a statistical benchmark [56, 57]. While in the other MHC's all patients received regular CBT, in this MHC 50% of the patients had received the minimal intervention before they started with CBT. A possible explanation for the lower effect sizes is that additional CBT after unsuccessful treatment requires different skills from the therapist compared to delivering regular CBT. After unsuccessful treatment it is not necessary to follow the complete protocol. Patients require additional support for specific elements of the treatment. As a consequence the role of the therapists changes, they have to attune more to the specific needs of the patient. Therefore in a next implementation project we recommend first to start with implementation of regular CBT. After one year of experience with regular CBT, therapists can be trained in the minimal intervention. At this point therapist will have gained the skills and knowledge to carry out 'additional' CBT after an unsuccessful minimal intervention.

Wiborg et al. found some evidence for a therapist effect. This means that some therapists have better results than others [58]. Less favourable attitudes of therapists towards the use of treatment manuals predicted less effective treatments. However, the setting where the treatment was delivered could also explain the variation in therapist efficacy, as less favourable attitudes and less effective treatments were within the same treatment setting. Additionally, it has to be mentioned that this MHC was the only MHC who implemented CBT in the context of stepped care [58], suggesting the implementation scenario may affect the results.

The third step in a model of stepped care for CFS, referring patients to a specialised tertiary treatment setting, has not yet been systematically examined. In the implementation study, described in chapter 6 [57], all patients who did not benefit from treatment had the option to receive additional treatment in a specialised setting. Only a few patients were actually referred. When investigating the reasons behind this, most therapists did not ask their non-responders if they preferred additional treatment. Due the limit number of referrals it is impossible to draw conclusions. Future research should also address this issue.

Cost effectiveness of implementation

If decision makers want to judge whether implementation of stepped for CFS is advisable, they need, besides information about the effectiveness of stepped care, information about

the costs and benefits. Several studies have examined the cost-effectiveness of behavioural treatments for chronic fatigue and CFS [59-62]. Results were not complete univocal but indicate that CBT for chronic fatigue or CFS might be cost-effective for society compared to care as usual. From a healthcare perspective the cost outcome ratio was more costly but also more effective than before. The proportion of the positive cost outcome ratio depended on how much value was placed on a recovered CFS patient. An explorative calculation of implementation of stepped care in an MHC showed that after a period of initial investment stepped care for CFS is cost effective for an MHC [63]. These data suggest, that implementing stepped care CFS in an MHC is cost-effective.

National implementation of stepped care for CFS

Our research group developed a plan for nationwide implementation of CBT for CFS. The plan provided a gradually implementation of stepped care for CFS. First, therapists will be trained in regular CBT for CFS. After finishing the training therapists receive supervisory sessions for at least one year. Additional, national education meetings will be organised twice a year. During the first two years each setting will receive additional support to stimulate recruitment of patients, contact with general practitioners and medical specialist, and publications in local newspapers. Also the support will include monthly feedback about the monitoring data. At each setting a person will be trained to supervise his/her colleagues. The aim is that each setting will be able to continue treatment of CBT for CFS after the implementation project. Second, after one year, therapists will be trained to carry out the minimal intervention. An internet based version of the minimal intervention will be developed, implemented and tested on efficacy.

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7

Summary

Chronic fatigue syndrome (CFS) is characterised by severe and medically unexplained fatigue, lasting at least six months and leading to functional impairments in daily life. Other symptoms of CFS include non-restorative sleep, post-exertion malaise, headaches, muscle pain, multi-joint pain, sore throat, tender lymph nodes, and impaired concentration or memory. Cognitive behaviour therapy (CBT) for CFS is an effective treatment. CBT is aimed at changing fatigue related cognitions and behaviours. CBT for CFS is developed in specialised treatment facilities. Previous research has shown that CBT for CFS can be successfully implemented in a mental health care centre (MHC). However, wider implementation is hampered by the fact that CBT for CFS is an intensive treatment, requiring licensed cognitive behaviour therapists. Therefore treatment capacity in the Netherlands is limited and treatment facilities cannot meet the demand for CBT for CFS. The studies described in this dissertation increase our knowledge about how to increase treatment capacity for CFS (chapter 3-6). The problem of under diagnosis of CFS by general practitioners is investigated in chapter 2.

In *chapter 1* a general introduction to CFS and the presented studies is given. *Chapter 2* describes a cohort study in a general practice. It investigated to what extent CFS is diagnosed by general practitioners (GPs). Patients visiting the practice in a period of four weeks were asked to complete a fatigue questionnaire. In addition, patients who had presented fatigue as main complaint one year ago were approached and asked to fill out the same questionnaire. Almost a third of the patients visiting their GP reported fatigue. Of the patients presenting complaints of fatigue one year ago, 50% still reported fatigue. In the prospective cohort, 2% (18/500) of the patients fulfilled the US Centers for Disease Control and Prevention criteria for CFS based on their response to the questionnaire. In the retrospective cohort, 8% (19/111) of the patients could be classified as CFS on the basis of the questionnaire. Only one person was actually diagnosed by the GP as having CFS. The results of this study suggest that GPs have difficulties in diagnosing CFS. There is a discrepancy between the number of patients that might be considered as suffering from CFS and the actual number of patients that is diagnosed with CFS. This discrepancy is suggestive for under diagnosis of CFS, leading to withholding effective treatment from patients. Based on the information in the electronic medical files, GPs often interpret fatigue as a symptom caused by psychosocial problems. They expect that attention limited to the somatic aspects of fatigue, hinders the solution of the psychosocial problems. The data of our study shows that it is necessary to develop a model of support for GPs. This can be achieved by providing instruments to assess CFS and training of GPs how to diagnose CFS .

There is evidence that not all CFS patients need an intensive CBT intervention. For a subgroup of patients, a minimal intervention suffices. This makes it possible to develop a

model of stepped care for CFS. In stepped care, more intensive treatments are reserved for patients who do not benefit from simpler low-intensity treatments. The model of stepped care for CFS distinguishes two levels. As a first step, guided self-instruction is offered to the patient. Next, as a second step, the patient receives face to face CBT. *Chapter 3* describes a randomised noninferiority study which tested the effectiveness and efficiency of stepped care for CFS. A total of 171 CFS patients are randomly allocated to stepped care or care as usual. Care as usual encompassed CBT after a waiting period. An intention to treat analysis showed no significant differences between the two interventions. Both conditions were equivalent in reducing fatigue severity and disabilities, and increasing physical functioning. When guided self-instruction was not sufficient, fewer sessions of CBT were required in subsequent treatment. The total therapist time needed to treat a patient was significantly less in the stepped care condition compared with care as usual. It is concluded that stepped care is as effective as CBT and more time-efficient.

As mentioned, treatment capacity for CFS is lacking. A minimal intervention based on CBT for CFS, guided self-instruction, is shown to be effective when delivered at a tertiary treatment facility with guidance of qualified cognitive behavioural therapists. Implementing guided self-instruction in a community-based MHC will increase the treatment capacity for CFS patients. *Chapter 4* evaluates the effectiveness of guided self-instruction for CFS implemented in an MHC. In a randomised controlled trial it is assessed whether psychiatric nurses, novices with respect to CBT and the treatment of CFS, are able to deliver this treatment successfully. Patients are randomly assigned to either guided self-instruction or a waiting list. Primary outcome variables–fatigue severity and physical and social functioning–are assessed at baseline and directly following the waiting period or intervention. After six months, patients who followed guided self-instruction reported a significantly larger decrease in fatigue compared to the waiting list. There were no significant differences in physical and social functioning. A subgroup of patients with physical disabilities at baseline showed a significant decrease in both fatigue and physical functioning following the intervention. Controlled effect sizes for fatigue severity and physical functioning were similar to those in the previous trial testing the effectiveness of guided self-instruction for CFS. To conclude, the results of this study suggest that guided self-instruction for CFS, delivered by trained and supervised psychiatric nurses, can be implemented successfully in an MHC.

The efficacy of guided self-instruction can be enhanced if it is known which patients will benefit from the intervention. This will also increase the efficiency of the treatment. The study described in *chapter 5* is aimed to identify moderators of the treatment response. Moderators are variables that strengthen or weaken the response to treatment. Potential

moderators are selected from the literature. To identify whether the selected variables moderated the effect of the intervention on fatigue at post-treatment assessment, linear and logistic regression analyses are used to test for significant interactions. Data obtained from two randomised controlled trials–evaluating the efficacy of guided self-instruction for CFS–are combined to test the potential moderators. Patients who were younger, had lower levels of depressive symptoms, and who had a lower tendency to avoid activity benefited more from the intervention than older patients and patients with higher levels of depressive symptoms and a stronger tendency to avoid symptoms. Guided self-instruction is exclusively aimed at cognitions and behaviours that perpetuate fatigue. Patients with severe depressive symptoms may need more specific interventions aimed at the reduction of these depressive symptoms in order to profit from guided self-instruction. Therefore we suggest that patients with substantial depressive symptoms be directly referred to regular CBT.

Besides the development of a model of stepped care for CFS, implementation of guided self-instruction in an MHC and the identification of moderators of treatment response, wider implementation of regular CBT for CFS can increase the treatment capacity. *Chapter 6* focuses on the treatment effect of CBT of CFS after implementation in three MHCs. We evaluated whether community based MHCs are able to implement or sustain CBT for CFS with the help of an implementation manual. The MHC that wanted to continue to use CBT, was able to carry on the treatment effectively. The other two MHCs had problems with the implementation of CBT for CFS. Therefore additional support by experts in CFS was needed. Implementation success was defined as including at least 40 patients for the treatment program of whom more than 30 had to complete a post-treatment assessment. Patients outcomes are documented with validated questionnaires for fatigue and physical functioning. With additional support, all MHCs were able to fulfill the success criteria. The treatment effects were similar to those found in randomised controlled trials testing the efficacy of CBT. Only the MHC which implemented CBT in the context of stepped care, showed lower treatment effects that the treatment effects found in the other trials. The most important lesson learned from this project is that MHCs can effectively treat CFS with CBT providing that there is sufficient support from specialists in the treatment of CFS.

The general discussion, *chapter 7*, considers the consequences of the findings of the previous chapters for the treatment for CFS. In Part I of the discussion the practical implications of the findings are discussed. Part II describes how the findings relate to the literature on CFS. The discussion ends with a plan for national implementation of stepped care for CFS. According to this plan the patient first receives guided self-instruction, if necessary followed by additional face to face CBT. National implementation of stepped care for CFS means that CFS patients will receive adequate treatment in their own region.

Samenvatting

Het chronisch vermoeidheidssyndroom (CVS) wordt gekenmerkt door lichamelijk onverklaarde ernstige vermoeidheid die langer dan 6 maanden aanhoudt. De vermoeidheid leidt tot substantiële beperkingen in het dagelijks leven. Vaak hebben CVS patiënten naast vermoeidheid ook andere klachten zoals spierpijn, gewrichtspijn, hoofdpijn, slaapklachten en concentratie- of geheugenproblemen. Cognitieve gedragstherapie (CGT) is een behandeling voor CVS waarvan de effectiviteit is aangetoond. De behandeling is gericht op het veranderen van opvattingen en gedrag die de vermoeidheid in stand houden. CGT voor CVS is ontwikkeld in gespecialiseerde behandelcentra. Eerder onderzoek liet zien dat CGT voor CVS succesvol in een GGZ-instelling geïmplementeerd kan worden. Idealiter zou men deze implementatie uitbreiden, maar doordat CGT voor CVS een intensieve therapie is, waarvoor getrainde cognitief gedragstherapeuten nodig zijn, is dit lastig te realiseren. Mede hierdoor is de behandelcapaciteit in Nederland niet toereikend. De vraag naar CGT voor CVS is groter dan het aanbod. De studies die in dit proefschrift worden beschreven dragen bij aan de kennis over hoe we de behandelcapaciteit kunnen uitbreiden (*hoofdstuk 3 t/m 6*). Het probleem van onderdiagnostiek van CVS in de huisartsenpraktijk is onderzocht in *hoofdstuk 2*.

In *hoofdstuk 1* wordt een inleiding gegeven over CVS en worden de achtergronden van de beschreven studies besproken. *Hoofdstuk 2* beschrijft een cohort studie, uitgevoerd in een huisartsenpraktijk. Het doel van deze studie was om vast te stellen of huisartsen de diagnose CVS stellen bij patiënten die hiervoor in aanmerking komen. Gedurende 4 weken is aan alle spreekuurbezoekers gevraagd een korte vragenlijst over vermoeidheid in te vullen. Daarnaast zijn patiënten die een jaar eerder de huisartsenpraktijk hadden bezocht met als primaire klacht vermoeidheid, aangeschreven met het verzoek dezelfde vragenlijst in te vullen. Bijna een derde van de spreekuurbezoekers gaf aan vermoeid te zijn. Van de patiënten die een jaar eerder last hadden van vermoeidheid, had 50% dit nog steeds. In het prospectieve cohort voldeed 2% (18/500) van de spreekuurbezoekers aan de consensus criteria van het US Centre for Disease Control voor CVS. In het retrospectieve cohort gold dit voor 8% (19/111) van de patiënten. Slechts één patiënt was daadwerkelijk gediagnosticeerd als CVS. Deze resultaten laten zien dat huisartsen minder vaak dan verwacht, op grond van de klachten van de patiënten, de diagnose CVS stellen. Het verschil tussen het aantal patiënten dat is gediagnosticeerd en het aantal patiënten waarbij die diagnose had moeten worden gesteld kan duiden op het onderdiagnosticeren van CVS hetgeen leidt tot onderbehandeling. Op grond van de informatie in het medisch dossier bleken huisartsen vermoeidheid vaak als een onderdeel van psychosociale problematiek te interpreteren in plaats van als een op zichzelf staande klacht. Aandacht voor de (somatische aspecten van) vermoeidheid, zou het aanpakken van de psychosociale problemen hinderen. Het is

nodig huisartsen hulpmiddelen te verschaffen zodat zij wanneer dat gerechtvaardigd is de diagnose CVS kunnen stellen. Door het ontwikkelen van meetinstrumenten om CVS vast te stellen en huisartsen te trainen in het stellen van de diagnose CVS kan de diagnostiek van dit syndroom in de huisartsenpraktijk worden verbeterd.

Eerder onderzoek heeft laten zien dat niet alle CVS patiënten een intensieve cognitieve gedragstherapie nodig hebben. Een aantal patiënten heeft aan een minimale interventie al genoeg. Vanuit deze bevinding is een model van getrapte zorg voor CVS ontwikkeld. In een model van getrapte zorg krijgen patiënten een intensievere behandeling aangeboden, als een minder intensieve behandeling niet geslaagd is of als vooraf al duidelijk is dat zij daar niet van zullen profiteren. Getrapte zorg voor CVS bestaat uit (1) zelfbehandeling met e-mail ondersteuning, zonodig aangevuld met (2) individuele reguliere CGT. *Hoofdstuk 3* beschrijft de uitkomsten van een gerandomiseerde gecontroleerde studie naar de effectiviteit en efficiëntie van getrapte zorg voor CVS. Patiënten met CVS (*n* = 171) werden willekeurig toegewezen aan ofwel getrapte zorg ofwel reguliere zorg. Reguliere zorg bestond uit CGT na een wachtperiode. Een intention-to-treat-analyse liet geen significante verschillen zien tussen de twee interventies. Beide leiden tot een significante afname van vermoeidheidsklachten en beperkingen. Als zelfbehandeling, de eerste stap van getrapte zorg voor CVS, niet het gewenste resultaat opleverde, hadden patiënten minder sessies individuele CGT nodig om alsnog te profiteren van behandeling. Ook was de tijd die een therapeut nodig had om een patiënt te behandelen met getrapte zorg significant minder dan tijdens reguliere zorg. Getrapte zorg voor CVS is dus even effectief als CGT, maar wel efficiënter.

De behandelcapaciteit van CGT voor CVS is niet toereikend. Onderzoek heeft aangetoond dat zelfbehandeling, begeleid door cognitieve gedragstherapeuten en uitgevoerd in een specialistisch centrum, leidt tot een afname van vermoeidheidsklachten en beperkingen in vergelijking met een wachtlijst. Als het mogelijk is om zelfbehandeling te implementeren in andere zorginstellingen, kan de behandelcapaciteit substantieel toenemen. *Hoofdstuk 4* beschrijft de resultaten van een implementatieproject waarin zelfbehandeling, een minimale interventie, werd geïmplementeerd en op effectiviteit getoetst in een GGZ-instelling. In een gecontroleerde en gerandomiseerde studie werd nagegaan of sociaal psychiatrisch verpleegkundigen, waarvan sommigen met beperkte gedragstherapeutische ervaring, in staat zijn de minimale interventie met succes uit te voeren. Patiënten werden toegewezen aan zelfbehandeling of werden geplaatst op een wachtlijst. De primaire uitkomstmaten, ernst van vermoeidheid en ernst van fysieke en sociale beperkingen, werden voorafgaand en na afloop van de interventie en de wachtperiode gemeten. Na 6 maanden waren

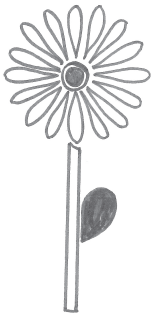
patiënten die de interventie hadden gevolgd significant minder moe dan de patiënten in de wachtlijst conditie. Wat betreft fysieke en sociale beperkingen werden er geen significante verschillen gevonden tussen de twee condities. Echter, patiënten die voorafgaand aan de interventie last hadden van fysieke beperkingen rapporteerden zowel verbetering van vermoeidheid als vermindering van beperkingen. De gevonden effecten zijn vergelijkbaar met de eerder genoemde studie waarin de zelfbehandeling werd begeleid door cognitieve gedragstherapeuten. Onze conclusie is dat de minimale interventie uitgevoerd door getrainde en gesuperviseerde sociaal psychiatrisch verpleegkundigen geïmplementeerd kan worden in de GGZ.

De effectiviteit van zelfbehandeling voor CVS kan vergroot worden als we weten welke patiënten de meeste kans hebben om te profiteren van de behandeling. De behandeling wordt hiermee ook efficiënter. De studie beschreven in *Hoofdstuk 5* richt zich op het voorspellen van behandeluitkomsten na zelfbehandeling door het identificeren van moderatoren. Een moderator is een variabele die de richting en de sterkte van de behandeluitkomst voorspelt. Potentiële moderatoren van zelfbehandeling voor CVS werden geselecteerd op basis van de literatuur. Vervolgens werd met behulp van regressie analyses getoetst of deze variabelen het effect van zelfbehandeling konden voorspellen. Om dit te evalueren werden de gegevens van twee gerandomiseerde gecontroleerde studies waarin de effectiviteit van zelfbehandeling werd getoetst, samengevoegd. Patiënten met CVS die jonger waren, minder last hadden van depressieve symptomen of minder geneigd waren om activiteiten te vermijden, behaalden betere uitkomsten na behandeling. Zelfbehandeling is uitsluitend gericht op opvattingen en gedragingen die de vermoeidheid in stand houden. Patiënten met ernstige depressieve symptomen hebben mogelijk specifieke interventies nodig gericht op het verminderen van de depressieve symptomen om te kunnen profiteren van de interventie. Ons advies is daarom om patiënten met ernstige depressieve symptomen direct reguliere CGT aan te bieden.

Naast het ontwikkelen van getrapte zorg, de implementatie van zelfbehandeling in een GGZ-instelling en het identificeren van patiënten die de grootste kans hebben om te profiteren van zelfbehandeling, kan uitbreiding van het reguliere CGT aanbod ook zorgen voor een toename van de behandelcapaciteit. *Hoofdstuk 6* beschrijft de behandelresultaten van CGT voor CVS bij implementatie in drie GGZ-instellingen. Bij één instelling was de vraag of zij de reeds geïmplementeerde behandeling op een vergelijkbaar niveau zonder hulp konden voortzetten. De overige twee instellingen hadden CGT voor CVS zelfstandig geïmplementeerd aan de hand van een handleiding. De eerste instelling was in staat het zorgaanbod op een vergelijkbaar niveau uit te voeren, de andere twee instellingen hadden

problemen met de implementatie van CGT voor CVS. Extra ondersteuning van deskundigen bleek noodzakelijk. De vooraf vastgestelde succescriteria voor implementatie, het werven van tenminste 40 patiënten waarvan 30 of meer de behandeling hadden afgerond (inclusief nameting), werden mede door de extra begeleiding door alle drie de instellingen behaald. De behandeluitkomsten werden voor en na de behandeling gemeten met gevalideerde vragenlijsten voor vermoeidheid en beperkingen. De effectiviteit van de behandeling in de GGZ instellingen kwam overeen met die van CGT voor CVS in eerdere gerandomiseerde studies. De instelling waarbij naast reguliere CGT gelijktijdig de minimale interventie werd geïmplementeerd, had minder gunstige resultaten na behandeling dan de overige twee instellingen. Het belangrijkste leerpunt van dit praktijkproject is dat GGZ-instellingen in staat zijn om CGT voor CVS zelfstandig op een kwalitatief hoog niveau aan te bieden, mits er bij de start voldoende ondersteuning aanwezig is door specialisten in de behandeling van CVS.

In *hoofdstuk 7* worden de resultaten uit de voorgaande studies bediscussieerd. In het eerste deel van de discussie worden de praktische implicaties van de studies besproken. In het tweede deel van de discussie zijn de resultaten van de studies vergeleken met de internationale literatuur over diagnostiek en behandeling van CVS. De discussie wordt afgesloten met een plan voor landelijke implementatie van getrapte zorg voor CVS. In dit model ontvangt een patiënt met CVS eerst de minimale interventie, zonodig gevolgd door individuele CGT. Het is wenselijk om dit model van getrapte zorg voor CVS landelijk te implementeren, zodat het straks voor iedere CVS patiënt mogelijk is om in zijn of haar regio een effectieve behandeling te ontvangen.



List of publications

Publications in international journals

Goedendorp M.M., van der Werf S.P., Bleijenberg G., **Tummers M.**, Knoop H.(2013) Does neuropsychological test performance predict outcome of cognitive behavior therapy for Chronic Fatigue Syndrome and what is the role of underperformance? *Journal of Psychosomatic Research*,75(3):242-248

Tummers M., Knoop, H., van Dam, A., Bleijenberg, G. (2013) Moderators of the treatment response to guided self-instruction for chronic fatigue syndrome. *Journal of Psychosomatic Research*, 74(5): 373-377

Tummers M., Lucassen, P.L., Wiborg, J.F., Bleijenberg, G. (2013) The challenge of diagnosing CFS in primary care. *International Journal of Clinical Practice*, 67(5): 489

Tummers M., Knoop, H., van Dam, A., Bleijenberg, G. (2012) Implementing a Minimal Intervention for Chronic Fatigue Syndrome in a Mental Health Centre: a Randomized Controlled Trial. *Psychological Medicine*, 42(10): 2205-2215

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Publications in national journals

Tummers M., Knoop, H. Bleijenberg, G. (2011) Getrapte zorg voor het chronisch vermoeidheidssyndroom. *Gedragstherapie*, 44, 69-81.

Tummers M., Knoop, H., van Dam A. Wiborg, J.F.W., Wensing, M., Bleijenberg, G. (2011) Noodzaak van landelijke implementatie van getrapte zorg voor het chronisch vermoeidheidssyndroom. *Gedragstherapie*, 44, 83-93.

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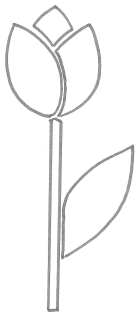

Dankwoord

Misschien is het je al opgevallen dat er in dit proefschrift verschillende bloemen staan. Waarom? Omdat ik vind dat een bloem een goede metafoor is voor mijn promotietraject. Op de eerste plaats staat de bloem symbool voor de patiënten, die hopelijk door het volgen van de behandeling weer in de bloei van hun leven staan. Ten tweede staat de bloem centraal voor het werk zoals beschreven in dit proefschrift. Het zaadje 'implementatie van behandeling voor CVS' dat we gepland hebben is uitgegroeid tot een prachtige tulp 'behandeling voor iedereen in zijn of haar omgeving'. Maar het belangrijkste symbool waar de bloem voor staat is dat de bloem alleen kan groeien en bloeien door verzorging, aandacht en liefde. Ik ben de mensen om mij heen dankbaar voor de zorg, aandacht en liefde die ik tijdens het schrijven van dit proefschrift heb mogen ontvangen. Een aantal mensen wil ik in het bijzonder bedanken.

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Mijn promotor en copromotor. **Gijs**, toen wij elkaar in 2007 voor het eerst ontmoetten had ik nooit gedacht dat dit proefschrift het uiteindelijke resultaat zou zijn. Voor jou was dat echter al snel duidelijk, te concluderen uit het feit dat je mij na ons tweede gesprek een baan aanbood. Ik heb de afgelopen jaren veel van je geleerd. De belangrijkste vaardigheden zijn misschien wel 'blijf kritisch', 'groot denken' en 'onderbouw je keuzes'. Drie dingen waar ik nog dagelijks de vruchten van pluk. **Hans**, samen met Gijs vorm jij de stabiele begeleiding die je als promovendus wenst. Je hebt me geleerd om niet te verzanden in details, maar me te richten op de grote lijn. Ik wil je danken voor je vertrouwen, op het moment dat er tegenslagen waren was jij altijd in staat om te relativeren en de positieve kanten te belichten.

Patiënten, therapeuten en sociaal psychiatrisch verpleegkundigen

Wat betreft de organisatie waren sommige onderzoeken een behoorlijke klus, maar het meeste en zwaarste werk is verricht in de praktijk. Van sommige patiënten weet ik dat vermoeidheid en de daarbij behorende beperkingen niet langer meer een issue zijn. Voor de anderen hoop ik dat deelname aan de onderzoeken iets heeft opgeleverd, al is het misschien niet het gewenste resultaat. Dank voor jullie inzet. Ook de therapeuten van het Nijmeegs Kenniscentrum Chronische Vermoeidheid (**Annemarie, Gerrie, Hans, Hein, Henriëtte en Thea**) en de sociaal psychiatrisch verpleegkundigen van de GGZ Westelijk Noord-Brabant (**Anne-Marie, Annette, Claire, Esther, Frans, Karla, Rita en Robert**) ben ik veel dank verschuldigd. Regelmatig kregen jullie van mij mailtjes en/of telefoontjes met betrekking tot gegevens die ontbraken en iedere keer waren jullie weer bereid om het voor mij uit te zoeken en erachteraan te gaan. Sociaal psychiatrisch verpleegkundigen voor jullie was het terrein van het chronisch vermoeidheidsyndroom en de daarbij behorende behandeling onbekend. Ik heb er bewondering voor hoe jullie je de behandeling hebben eigen gemaakt

en er kleur aan hebben gegeven. Het resultaat hiervan is terug te zien in het aantal herstelde patiënten. Tevens wil ik de therapeuten werkzaam bij GGZ Westelijk Noord-Brabant, PsyQ Den Haag en GGnet bedanken voor hun inzet en het behandelen van patiënten.

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Leden van de manuscriptcommissie

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Collega's van het nijmeegs kenniscentrum chronische vermoeidheid

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Over de auteur

Over de auteur

Marcia Tummers werd op 6 mei 1984 geboren te Geleen en groeide op in het nabijgelegen Elsloo. In 2002 behaalde zij haar atheneum diploma aan het Groenewald College te Stein. Hierna ging zij Biomedische Wetenschappen studeren aan de Radboud Universiteit Nijmegen.

Voor haar hoofdvak bewegingswetenschappen liep zij haar eerste wetenschappelijke stage op de afdeling Fysiologie van het Universitair Medisch Centrum (UMC) St Radboud. Deze stage werd afgesloten met het behalen van een eerste prijs tijdens het Belgisch–Nederlands studentencongres der bewegingswetenschappen. Tijdens de master fase liep zij achtereenvolgens stage bij de 'Miami project to Cure Paralysis' in Miami, en de afdeling kinderfysiotherapie van het UMC St Radboud.

Na het behalen van haar diploma in 2007 werd zij aangesteld als junior onderzoeker op het Nijmeegs Kenniscentrum Chronische Vermoeidheid van het UMC St Radboud. Zij deed onderzoek naar getrapte zorg voor het chronisch vermoeidheidssyndroom. Het resultaat hiervan is te lezen in dit proefschrift. Naast het onderzoek was ze gedurende een aantal jaar actief als voorzitter en algemeen lid in de PhD council van het Nijmegen Centre for Evidence Based Practice.

Na haar promotieonderzoek bleef Marcia als onderzoeker verbonden aan het Nijmeegs Kenniscentrum Chronische Vermoeidheid. Ze hield zich bezig met een landelijk implementatieproject van getrapte zorg voor het chronisch vermoeidheidssyndroom. Daarnaast is zij in april 2012 gestart als onderzoeker op de afdeling Health Evidence eveneens verbonden aan het UMC St Radboud. Op deze afdeling is zij betrokken bij verschillende onderzoeksprojecten die zich bezighouden met implementatie, gedeelde besluitvorming, patiëntvoorkeuren en personalized medicine. Ook geeft zij onderwijs aan studenten van de opleiding Geneeskunde en Tandheelkunde. Sinds mei 2013 is Marcia fulltime in dienst als post doc onderzoeker bij de afdeling Health Evidence.